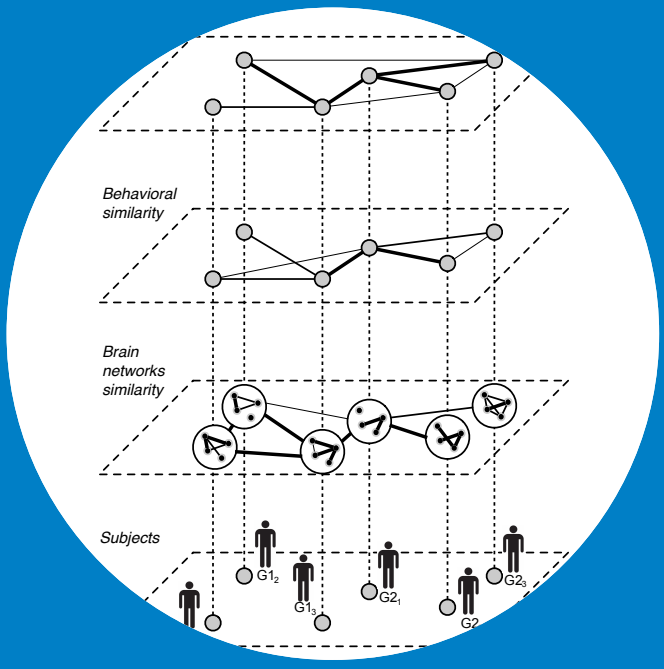
Department of Neuroscience and Biomedical Engineering

Dynamic similarity of brain activity in humans: from single areas to functional networks

The similarity of brain functioning between different people supports mutual understanding and reveals similar behavioral traits

Enrico Glerean



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Dynamic similarity of brain activity in humans: from single areas to functional networks

The similarity of brain functioning between different people supports mutual understanding and reveals similar behavioral traits.

Enrico Glerean

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Abstract

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Abstract

What makes us similar and different? The intriguing problem has been studied throughout the centuries by philosophers and scientists and affects the way we live our lives in relationship to the people around us. The brain can process the external world in a similar way across people and even across animal species, but the boundary between similar/different is a dynamic one that changes in space – "where" in the brain we are similar – and in time – "when" brain activity is similar between us. It has been possible to show how localized brain regions show varying levels of intersubject similarity during controlled and naturalistic experiments using functional magnetic resonance imaging. However, the temporal dimension – "when" brain activity is similar between two brains – has remained poorly explored. Furthermore, the brain is a network and the concept of network-level intersubject similarity poses novel challenges especially when considering inter-individual differences both between and within healthy and clinical populations. Here we studied how intersubject similarity of brain activity is modulated in time due to the content of the stimuli or to the psychological perspective that subjects take. These novel problems led to the development of new methods to quantify instantaneous similarity between brains. In addition, moving emphasis from local neuronal activity to distributed network activity, we addressed the challenge of defining the similarity between brain subnetworks to identify their intersubject similarity in relation to behavioural measures. In the first study we used videoclips to induce strong emotions during fMRI scanning and computed how time-varying intersubject correlation of brain activity was modulated by the emotional experience. Feeling similar emotions makes the brains tick in sync. In the second study we introduced novel measures for instantaneous brain similarity for local activity and for dynamic functional connectivity. In the third study we considered how taking different psychological perspectives is reflected in brain activity. Finally, in the fourth study we isolated functional brain networks of high functioning individuals with autism spectrum disorder and healthy controls while watching a feature film, and proposed a method to correlate the autism quotient and the configuration of brain subnetworks. The work presented here reflects recent developments in human non-invasive neuroscience, by stressing the importance of the temporal dimension from local activity dynamics to time-varying networks and the individuality of each brain in relationship to others. Mutual understanding and similarity of behaviour between individuals might be related to similarity of brain function and structure. Although the causality of such relationships might be difficult to disentangle, the current work proposes tools to quantify them.

Keywords brain, fMRI, intersubject similarity, phase synchronization, graph theory, functional connectivity, autism

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“We all live with the objective of being happy, our lives are all different and yet the same.”

The Diary of a Young Girl, Anne Frank

Preface

The work presented in this thesis was carried out at Department of Biomedical Engineering and Computational Science (BECS) – now Neuroscience and Biomedical Engineering department (NBE) – part of Aalto University School of Science. Doing a doctorate was an incredible coming-of-age story and I can never thank enough all the people who have been involved in this process.

The first and foremost "thank you" goes to Professor Mikko Sams for the support and guidance through the years, for being the ideal *boss*, but also beyond work and science as a great lover of music, art, good food and wine. The second acknowledgment goes to Academy Professor Riitta Hari, one of the most inspiring persons I have met, always ready to challenge everyone and everything for the true purpose of advancing science and knowledge. Thirdly, I wish to thank Iiro Jääskeläinen, Lauri Nummenmaa, and Juha Salmitaival: working with you has been smooth and easy, as if we have been knowing each other for years.

A warm "thank you" and a "sorry for the bad jokes" go to all current and past members of the Brain and Mind lab, especially to Juha Lahnakoski. I also want to thank Raj Kumar Pan and Jari Saramäki for introducing me to the fascinating world of network science and graph theory.

Special thanks to Elvira Brattico, Mari Tervaniemi, Petri Toiviainen, and Tuomas Eerola: it is because of you that I decided to go back to academic work-life.

I would like to thank all other colleagues that I have worked with and met at BECS especially Jouko Lampinen, Kimmo Kaski, Santo Fortunato, Aki Vehtari, Arno Solin, Simo Särkkä, Lauri Parkkonen, Laura Pyysalo, Eeva Lampinen, Mikko Hakala, guitar master Riku Linna and others from the Bayesian group and Complex Network group: it was truly inspiring to share the spaces with you as I believe that Bayesian and network modeling are the key methods for the future of neuroscience.

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This work would have not been possible without the financial support from the "Brain and Mind" doctoral program, aivoAALTO research project, and the Academy of Finland (National Centre of Excellence Program 2006–2011).

Finally, I would like to thank my parents and brother for always supporting my life decisions, despite me moving thousands of kilometers away from them.

Thanks to my dear friends around the world for support and encouragement throughout the years: there are too many of you to make a list although a special thanks goes to Eric Namour.

The biggest last “thank you” is going to my wife Niina and my son Edvin: your love and joy are the meaning of my life.

Espoo, November 4th, 2015

Enrico Glerean

Contents

List of Publications

This thesis comprises of three journal publications and one manuscript under review. Publications are referred to by their roman numerals.

I. Nummenmaa, L., Glerean, E., Viinikainen, M., Jaaskelainen, I. P., Hari, R., & Sams, M. (2012). Emotions promote social interaction by synchronizing brain activity across individuals. Proceedings of the National Academy of Sciences, 109(24), 9599–604. doi:10.1073/pnas.1206095109

II. Glerean, E., Salmi, J., Lahnakoski, J. M., Jääskeläinen, I. P., & Sams, M. (2012). Functional magnetic resonance imaging phase synchronization as a measure of dynamic functional connectivity. Brain Connectivity, 2(2), 91–101. doi:10.1089/brain.2011.0068

III. Lahnakoski, J. M., Glerean, E., Jääskeläinen, I. P., Hyönä, J., Hari, R., Sams, M., & Nummenmaa, L. (2014). Synchronous brain activity across individuals underlies shared psychological perspectives. NeuroImage, 100, 316–324. doi:10.1016/j.neuroimage.2014.06.022

IV. Glerean, E., Pan, R. K., Salmi, J., Kujala, R., Lahnakoski, J., Roine, U., Nummenmaa, L., Leppämäki, S., Nieminen-von Wendt, T., Tani, P., Saramäki, J., Sams, M., & Jääskeläinen, I. P. (2015). Reorganization of functionally connected brain subnetworks in high-functioning autism. Neurons and Cognition. http://arxiv.org/abs/1503.04851, 35 pages (Under revision in Human Brain Mapping)

Author's Contribution

Study I The candidate gathered the data, implemented the data analysis approaches, analyzed the data, and contributed to the writing of the manuscript, specifically related to the methods section. Assistance for the data acquisition was received from Mikko Viinikainen, Lauri Nummenmaa and Marita Kattelus. All co-authors gave valuable input during writing of the manuscript.

Study II The candidate designed the analysis method, analyzed the data and wrote the manuscript. All co-authors gave valuable input during writing of the manuscript.

Study III The candidate contributed to the design of the analysis method and to the writing of the manuscript, specifically related to the methods section. All co-authors gave valuable input during writing of the manuscript.

Study IV The candidate designed the data analysis approaches, analyzed the data and wrote the manuscript. All co-authors gave valuable input during writing of the manuscript.

List of Abbreviations and Symbols

ABIDE	Autism brain imaging data exchange
ACC	Anterior cingulate cortex
ACG	Anterior cingulum
ADI-R	Autism diagnostic interview revised
ADOS	Autism diagnostic observation schedule
AMYG	Amygdala
ANG	Angular gyrus
AQ	Autism quotient
ASD	Autism spectrum disorder
AUD	Auditory
BOLD	Blood-oxygen-level dependent
BST	Brainstem
CAL	Calcarine gyrus
CAU	Caudate
CG	Calcarine gyrus
CUN	Cuneus
DA	Dorsal attention
DCG	Middle cingulum
DM	Default-mode
eyeISC	Intersubject correlation of eye movements
FC	Functional connectivity
FDR	False discovery rate
FFG	Fusiform gyrus
fMRI	Functional magnetic resonance imaging

GLM	General linear model
GWAS	Genome wide association studies
HES	Heschl's gyrus
HIP	Hippocampus
HRF	Haemodynamic response function
I-IV	Cerebellar lobule I-IV
ICA	Independent component analysis
IFGoperc	Opercular inferior frontal gyrus
IFGtriang	Triangular inferior frontal gyrus
INS	Insula
IOG	Inferior occipital gyrus
IPL	Inferior parietal lobule
IPS	Intersubject phase synchronization
ISA	Intersubject analysis framework
ISBPS	Intersubject seed based phase synchronization
ISC	Intersubject correlation
ITG	Inferior temporal gyrus
IX	Cerebellar lobule IX
IX-vermis	Cerebellar vermis IX
LAN	Language
LG	Lingual gyrus
LING	Lingual gyrus
LOC	Lateral occipital cortex
MFG	Middle frontal gyrus
MNI	Montreal neurological institute
MOC	Medial occipital cortex
MOG	Middle occipital gyrus
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
MVPA	Multi-voxel pattern analysis
NAcc	Nucleus accumbens

NT	Controls ("neurotypical")
OFC	Orbitofrontal cortex
OLF	Olfactory cortex
ORBinf	Orbital inferior frontal gyrus
ORBmid	Orbital middle frontal gyrus
ORBsup	Orbital superior frontal gyrus
ORBsupmed	Orbital medial frontal gyrus
PAL	Pallidum
PCG	Posterior cingulum
PCL	Paracentral lobule
PCUN	Precuneus
PHG	Parahippocampal gyrus
PoCG	Postcentral gyrus
PPC	Posterior parietal cortex
PreCG	Precentral gyrus
PS	Phase synchronization
PUT	Putamen
REC	Gyrus rectus
ROI	Region of interest
ROL	Rolandic operculum
RSA	Representation similarity analysis
SAL	Salience
SBC	Seed based correlation
SBPS	seed based phase synchronization
SFGdor	Superior frontal gyrus
SFGmed	Medial superior frontal gyrus
SI	Scaled Inclusivity
SM	Sensorimotor
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SOG	Superior occipital gyrus

SPG	Superior parietal lobule
STG	Superior temporal gyrus
STS	Superior temporal sulcus
THA	Thalamus
TPJ	Temporoparietal Junction
TPOmid	Temporal pole (middle)
TPOsup	Temporal pole (superior)
TR	Repetition time
V	Cerebellar lobule V
V1	Visual primary
VI	Cerebellar lobule VI
VI-vermis	Cerebellar vermis VI
VIIb	Cerebellar lobule VIIb
VIIIa	Cerebellar lobule VIIIa
VIIIa-vermis	Cerebellar vermis VIIIa
VIIIb	Cerebellar lobule VIIIb
VIIIb-vermis	Cerebellar vermis VIIIb
VIS	Visual extrastriate
VTC	Ventral temporal cortex
VTL	Ventro-temporal limbic
X	Cerebellar lobule X
X-vermis	Cerebellar vermis X
XI	Cerebellar crus I
XII	Cerebellar crus II
XII-vermis	Cerebellar vermis crus II

1. Introduction

1.1 The same... but different, yet the same

The concept of similarity

Similar: adj. Having a resemblance in appearance, without being identical (Oxford Dictionary). The concept of similarity seems to be defined by what it is not. It is not an identity. Furthermore, the dictionary uses the word "resemblance" which is defined as "having a similar appearance". Oh dear, we are in a loop! If two things are similar they are not identical, are they different then? Thesaurus does not agree with this logic since "different" is an antonym of "similar". How can we possibly build any solid science on a concept that our words fail to describe?

The concept of similarity is present in multiple domains: mathematics, music, linguistics, biology just to name a few (for a formal concept analysis see for example Falan, 2010). We understand that similarity is *almost* an identity. In philosophy identity – or "sameness" or equality – dates back to Leibniz and his modern formulation of the Law of identity (Mates, 1989, p. 1): x is the same as y if and only if every predicate true of x is true of y as well. While in mathematics it seems trivial to understand the concept of identity, its extensions are touching our daily lives: cultural identity, social identity, digital identity, identity theft, and so on. All these scenarios require a contextual definition of what makes two entities identical: Is it the same cultural background? Having the same social security number?

If similarity is *almost* an identity, we need a measure to quantify the "*almost*". In mathematics, similarity measures are often derived from distance measures or norms (Chen et al., 2009) and have been adopted also in the context of psychology for a long time (Tversky, 1977). If two quantifiable entities in a multi-dimensional space – called vectors – have a distance equal to “0” (zero), then we can call them identical and they can be assigned a similarity score equal to “1” (one). A similarity metric could then be seen as a real number between zero and one for describing when two things are completely different or exactly the same, and everything in between. A distance metric is dependent on the number of dimensions where the entities are defined. If we consider two points in the three dimensional space with coordinates (1,1,1) and (1,1,1000), they have distance equal to zero if we consider only the first two dimensions, but with the third dimension added we see that they are far apart. With more complex entities these dimensions are called features (Tversky,

1977). Different living organisms share lots of similar features. We don't need to read Darwin to realize that humans and many other animals have dozens of similar features: the same number of eyes, a mouth, a nose and a brain with two hemispheres. Furthermore we observe similar behavior in similar species as well as across species. But how many features are needed to quantify the similarity between two individuals? Is it enough to have *almost* the same DNA? Is it enough to have *almost* the same brain substructures to obtain *almost* the same behavior?

1.2 Great minds think alike

Similarity of brains

There are no good answers to the question what features we should consider in comparing similarity of two individuals. The historical debate of nature *vs.* nurture had the egregious Sir Francis Galton as its promoter. Apart from discovering things like statistical variance, correlation and regression analysis, Sir Galton was also a pioneer in behavioral genetics by running the first twin studies in history to understand the inheritance of abilities whether it is written in our nature (inherited genes) or nurture (the environment where we live) (Gillham, 2001). Nowadays we understand that the picture is more complex than just nature and nurture since stochastic noise and the “epigenetic landscape” (Mitchell, 2007) play a role in creating truly unique individuals. Differences in human behavior, perception, reaction-times and their neuronal correlates have often been characterized as "noise" by psychologists and neuroscientists and are discarded during group averaging (Kanai and Rees, 2011). On the other hand, the field of differential psychology (Tyler, 1965), pioneered by Sir Galton himself, stresses the importance of the differences (and similarities) across individuals and started to study individual personality traits.

We could argue that perceiving the surrounding world in a similar way creates the basis for mutual understanding. If we both share the same representations for the color red and for the word "red", we are able to understand each other. If we both like the same music, it increases likelihood that we socially bond and become friends (Selfhout et al., 2009). This seems to imply that a prerequisite for mutual understanding – which not only means communication by language but also empathy and taking other’s perspective – is rooted in the similarity of human brain structure as well as in the similarity of its dynamics through which representations of concepts are processed (Pitt, 2013). With brain structure, inter-individual differences of grey matter volume and white matter tracts are significant predictors of reaction time, decision-making, conscious sensory perception, attention, intelligence and personality (Kanai and Rees, 2011). Brain structure however changes on slow temporal scales in the orders of months; it is then difficult to relate brain structure to fast changing behavior. A viable option is to use functional imaging to measure temporal dynamics of brain activity and consider the similarities of the measured signals. For example, functional magnetic resonance imaging (fMRI) has been successfully adopted to non-invasively show reliable brain activity across

healthy subjects who were watching a feature film in the scanner (Hasson et al., 2004). With intersubject correlation – a measure of inter-individual similarity of signals (see methods) – it is possible to quantify the across-subject similarity of each brain region in the response to the external stimulus (Hasson et al., 2010). The brain activity in sensory regions is relatively inter-subject similar, with the type of stimuli modulating the level of synchrony: The more structured is the stimulus, the larger the intersubject correlated areas in the brain, (Hasson et al., 2008a). However, it is more challenging to observe synchronization in areas involved in complex cognitive processes that are not necessarily synchronous across subjects.

Inter-individual differences are even more important when we consider mental disorders and their neuronal underpinnings. First of all, clinical studies always need a healthy control group, but what does it mean to have a healthy brain? What does it mean to be normal when it comes to brain structure and function? It has been argued that what we know about the healthy brain nowadays is mostly based on studying college students in their early twenties (Henrich et al., 2010): is this really a "neurotypical" brain? The word neurotypical is a term originated in the autism community as a label for "normal" people who are not diagnosed with autism spectrum disorder (ASD) to raise public awareness on the "neurodiversity", and increase acceptance of people with different brains like individuals with ASD.

Spectrum disorders, such as autism or schizophrenia spectrum, are characterized by the co-occurrence of multiple symptoms where two patients can present wide differences in behavior despite being diagnosed under the same label. Group averaging could wipe out differences between patients and healthy controls and lead to missing important clinical sub-types and inter-individual peculiarities, with the final result of inconclusive findings (Kanai and Rees, 2011). Autism for example covers a wide range of symptoms with core symptoms such as social and communication disturbances, and restricted or repetitive behavior (Lai et al., 2013). Genetic and imaging studies agree in characterizing ASD as a manifestation of subtle abnormalities in the brain connectivity of affected individuals (Hernandez et al., 2014) and there are no “typical” individuals with ASD. Recent brain imaging studies have not resulted in agreement on possible neuronal correlates of ASD due to the mixture of disagreeing findings (Maximo et al., 2014; Haar et al., 2014). Only recently researchers have started taking into consideration the full range of inter-individual idiosyncrasies in participants with ASD (Salmi et al., 2013; Byrge et al., 2015; Hahamy et al., 2015; Study IV from this thesis) recognizing that key areas involved in social perception and emotion processing, whose functioning is atypical in ASD, have a wide range of individual variance.

1.3 Tell me who you go with and I will tell you who you are

Network science: between and within individuals

Networks are omnipresent in biological and human made systems (Newman, 2003). At the large macroscopic scale, individuals form social networks (Hill

and Dunbar, 2003). Each of us belong to multiple overlapping networks which constitute the social environment where we live: the network of our friends, colleagues, relatives and so on (Ahn et al., 2010). Networks are nested into networks and within our skull we carry one of the most complex networks: the brain. Networks are at the core of complex systems and network science has become an important tool for studying the interaction between individuals as well as the interaction between brain areas (Sporns, 2010).

Networks – or graphs – are characterized by multiple nodes and links between them: nodes can be the people of a social network and links can be a zero/one relationship between each of them (is-a-friend, is-a-colleague, is-a-relative, etc.). A link can also be weighted like a similarity measure between the features of two individuals. The same is in the brain: a structural network of physical links (synapse) between nodes (neuron) on top of which the functional network dynamically evolves to form functional links between nodes that are not directly connected (Sporns, 2010) – Figure 1.

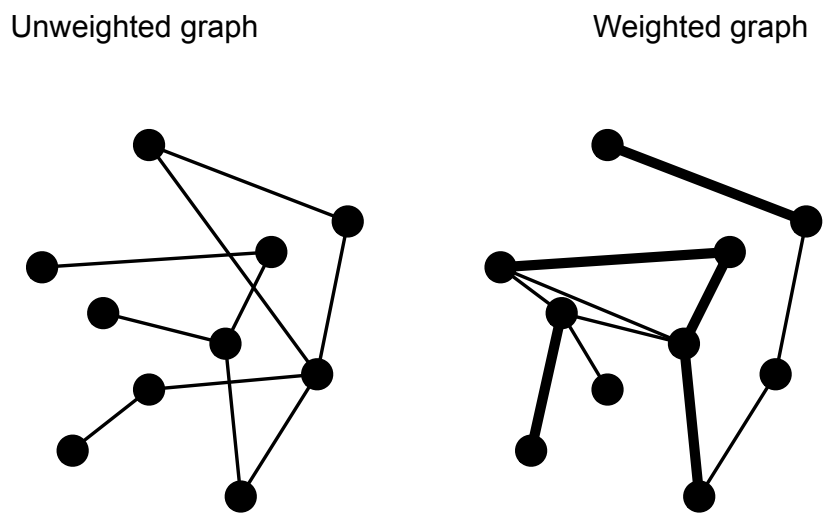

Figure 1. An unweighted graph (like in a structural brain network) and a weighted graph (like in a functional brain network).

Structural neuronal network – also known as connectome – can be studied in their fullness only in simple organisms like the worm c-elegans or the fruit fly (Plaza et al., 2014). With its 10^{10} neurons and 10^{14} connections, it is currently impossible to study the full connectome of the human brain. However, by sacrificing spatial resolution, human brain structural and functional networks can be studied non-invasively with resonance imaging (Craddock et al., 2013). By taking each area of the brain as a node, it is possible to estimate a functional network by computing the similarity between each pair of nodes activity time series. This simple approach – known as functional connectivity – is able to tell us which pairs of regions are oscillating in sync.

Serendipitously, in the early 1990s Bharat Biswal decided to calculate functional connectivity of a subject while being at rest during fMRI. This marked the birth of resting state functional connectivity (Biswal, 2012). By letting the subjects simply rest in the scanner, it is possible to estimate functional connectivity, which reflects the anatomical organization of human brain networks (Sporns, 2014). This led to multiple large-scale efforts of data collection and sharing (1000 FC, Human Connectome Project) and studies revealing the networks – also known as subnetworks, subgraphs, modules – of the human brain. Two studies from 2011 (Power et al., 2011; Yeo et al., 2011) used the resting state paradigm and network clustering to identify brain subnetworks. Both studies reliably identified a set of subnetworks: Visual, Somatomotor, Dorsal attention, Ventral attention, Limbic, Frontoparietal, Default (Yeo et al., 2011) – Figure 2.

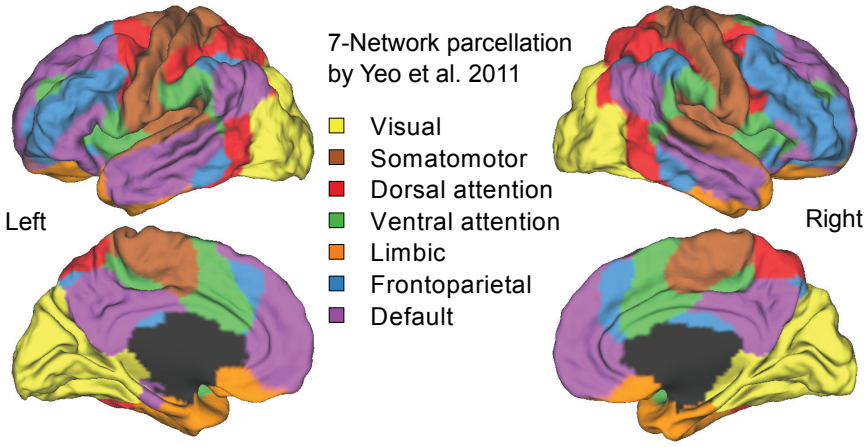

Figure 2. The seven subnetworks identified by Yeo et al (2011). Cerebellum and subcortical areas are not included and should be considered as their own subnetworks.

By modeling spontaneous (and task dependent) brain activity as a network with multiple nodes, graph theoretical properties of brain networks were calculated to identify important hubs, reveal the small-world/scale-free structure of the brain network and cluster multiple areas based on the connectivity patterns (Bullmore and Sporns, 2009, 2012).

However, comparison of inter-individual differences in networks is not trivial (Alexander-Bloch et al., 2012). Comparing the brain networks of two individuals can happen at multiple spatial resolutions, from the level of single links and nodes to the level of the whole network: networks that are similar at global level, might be very different at the level of subnetworks. Understanding which one is the optimal level for comparisons becomes fundamental when studying anomalous and idiosyncratic networks such as the brain of individuals with ASD.

1.4 Panta rhei

Brain and networks in time

Similarity however can also be considered in the temporal dimension. Everything changes in time and, as Heraclitus put it, "No man ever steps in the same river twice" (Graham, 2011). The world around us is dynamic but rarely such richness and complexity has been taken into cognitive experiments. Lifelike naturalistic stimuli, for example, movies (Hasson et al., 2004), narrated stories (Nummenmaa et al., 2014b), and music (Alluri et al., 2012), increase the ecological validity of neuroimaging studies and enable new type of research on higher-order cognitive functions such as temporal integration of information (Hasson et al., 2008b), memory performance (Furman et al., 2007), emotions (Nummenmaa et al., 2012), language comprehension (Smirnov et al., 2014) and social cognition (Lahnakoski et al., 2012a). Due to the time-varying nature of the stimuli, standard analysis methods based on averaging over many repetitions are not valid anymore. While there are successful attempts at modeling complex stimuli (Bartels and Zeki, 2004; Lahnakoski et al., 2012b; Alluri et al., 2012) data driven tools need to identify not only *where* in the brain there is consistent activation across subjects but also *when* such moments of inter-subject synchronization arises as a consequence of extrinsic stimulation or intrinsic mentalization processes.

The brain is a complex dynamic system that works at multiple time scales (Penttonen and Buzsáki, 2003): from the detection of directional hearing cues (~0.5 ms), to the slow spontaneous fluctuations during rest (~5 s) up to temporal scales of minutes for mood changes (Hari and Parkkonen, 2015). As a complex dynamical system, focusing on average activity assumes stationarity of the system while important instantaneous brain states might be more relevant to cognition and closer to how actually the brain work (Tagliazucchi et al., 2012; Chen et al., 2015). When enjoying a concert with all musical instrument playing in harmony or when using idioms such "being on the same wavelength", we all experience dynamic synchronization with the external world and with others. Synchronization is one of the most common ways of sharing information between entities of a system (Mesulam, 1990; Strogatz, 2004). It is then clear how important it is to quantify these time-varying phenomena to reveal mechanisms of mutual understanding across subjects as well as individual differences in healthy and clinical populations (Salmi et al., 2013).

The studies presented here demonstrate a collection of novel tools – the intersubject analysis framework – to specifically address the challenges of analyzing inter-individual differences during complex stimuli with emotional and social cues. From the level of single brain areas to the level of brain subnetworks, the studies aim at understanding the dynamic mechanisms of emotion processing, perspective taking, and to outline a solution for the mixed findings in the connectivity literature of ASD. The results reveal neuronal mechanisms on how and when brains are ticking in and out of synch with other brains, to facilitate interpersonal understanding and interaction.

2. Methods

In this chapter I describe the methods used in the four studies of this thesis, from data collection, to data preprocessing, analysis and modeling methods.

2.1 Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) is a widely used non-invasive brain research method. MRI is based on detecting changes in magnetic properties of hydrogen nuclei elicited by oscillating magnetic field applied at the resonance frequency of the nucleus in a strong magnetic field; spatial information is encoded by using magnetic field gradients. Extensive definitions and explanations are found in Huettel et al. (2004). What follows is an intuitive explanation on the lines of Hanson (2008).

Atoms of hydrogen – the most abundant atom in the human body – have a property called spin, which is their magnetic moment. Think of the magnet inside a compass that aligns to the planet earth's magnetic field, with one end pointing to the north and the opposite end to the south. Hydrogen atoms are tiny though, and a bit of heat (like room temperature) makes them shake and bounce so that their spins are pointing into all direction: The magnetic field of planet earth (~50 10^-6 Tesla) is too weak to make them align like compasses. However, if we then put hydrogen nuclei in a strong magnetic field (e.g. the 3 Tesla field that we measure inside an MRI scanner is 60,000 times stronger than earth's magnetic field), the spin of hydrogen atoms will align to the same direction of the field, as compasses do with planet earth's field by pointing towards the North Pole. If we continue with the compass metaphor, when we shake the compass the tip of the magnet will momentarily stop pointing to the north until after some time (relaxation time) when it will get back to equilibrium. The same is with hydrogen atoms inside a strong magnetic field: We "shake" them by giving them a pulse of electromagnetic energy. Atoms will move and when a magnet moves, it generates a radio wave that we are able to pick up with a receiver, just like getting a radio signal with your stereo. Like in the compass case, atoms will slowly go back to equilibrium and we can measure how long it takes for them to re-align with the external strong magnetic field. Different types of tissues have different concentrations of hydrogen so they will give different measurements in how fast they go back to equilibrium: white matter (with more water, hence with more hydrogen) will have a differ-

ent relaxation time than grey matter (with less hydrogen), so by contrasting them we are able to store them as gray-scale images with different intensities for each pixel. Brain MRI images however are volumes: they are obtained by collecting multiple two-dimensional images (slices) that cover the whole head. In the literature, pixels are called voxels to stress the three-dimensional nature of the data. An average voxel – a tiny cube with ~4mm edge – covers a volume of ~55 mm^3 containing 5.5 million neurons, 2.2–5.5 x 10^10 synapses, 22 km of dendrites and 220 km of axons (Logothetis, 2008).

2.2 Functional magnetic resonance imaging

Functional MRI (fMRI) can be thought as an extension of MRI by adding the temporal dimension. With fMRI, a pulse sequence shakes the direction of the hydrogen spins periodically every couple of seconds also know as repetition time (TR). This generates a periodically sampled signal for each voxel: a time series. As with any signal that is sampled (Shannon, 1949) we want to have a sampling frequency that is as high as possible (i.e. a very short TR) to avoid aliasing which results in distortions in the sampled signal. In practice, repetition time will inevitably depend on how fast spins can go back to their aligned status and on how many slices we want to collect to cover the whole head: the larger the number of slices, the longer the TR.

Rather than hydrogen however, fMRI measures the magnetic properties of blood. Part of blood in the brain is bound with oxygen (oxygenated hemoglobin) but the rest is not (deoxygenated hemoglobin). Hemoglobin transports oxygen from the lungs to the rest of the body, to participate in metabolism in organs. Oxygenated hemoglobin has a null magnetic spin, which means that it does not distort the measured MRI signal from areas with oxygenated blood. Deoxygenated hemoglobin however has non-null spin – it is like a magnet – and is then affecting the MRI signal by lowering the measurement. For these reasons, the signal recorded with fMRI is called the blood-oxygen-level dependent (BOLD) signal. But how is the blood oxygen concentration in the brain related to neuronal activity?

2.2.1 The BOLD signal

The relationship between BOLD signal and underlying neuronal activity is complicated (Logothetis, 2008; where not specified in this section, this is the information source). BOLD is an indirect measure of brain activity: by measuring consumption of oxygen in each voxel in the brain, we can infer that a voxel is or is not active. This relationship between neuronal activity and BOLD signal is called neurovascular coupling. The limitations of neurovascular coupling are not related to the fMRI method itself, but the actual physiology of the underlying neurons. Furthermore, being an indirect measure of neuronal activity, BOLD signal is affected by the flowing of blood in the brain, which is orders of magnitude slower than neuronal activity.

In a single voxel there are ~5 million neurons, meaning that each voxel reflects activity of a very large neuron population. The BOLD signal reflects neu-

romodulatory processes (inhibition and excitation) that are affecting the whole neuronal population. Neuromodulatory effects – due to, e.g., arousal, attention, memory – are also happening at the slow time scales of blood flow (tens of seconds) which makes fMRI the best tool to investigate such cognitive processes in association areas rather than simple sensory processing that can happen at time scales of milliseconds.

The correspondence between neuromodulatory processes and BOLD signal can be approximated by the haemodynamic response function (HRF; Buxton et al., 1998; Friston et al., 2000) which smoothens and delays the neuromodulatory signal (Figure 3).

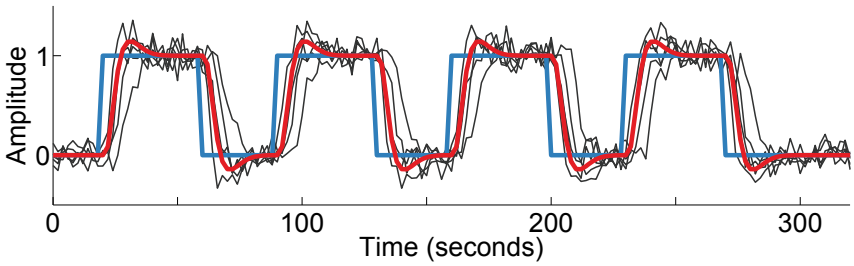

Figure 3. In blue an ideal neuromodulatory activity in an area that is periodically activated and deactivated (e.g. primary visual cortex during on/off visual stimulation). In red the ideal BOLD signal as predicted by the balloon model. In black responses of five hypothetical subjects with varying haemodynamic lag and noise.

Since the early days however, researchers have noticed the high unreliability of BOLD signal (Aguirre et al., 1998): even the same subject on the same day can have different HRF (BOLD within subject consistency across runs on the same day is ~46%, and in different days ~36%, Krieger et al., 2014). Furthermore HRF is also different in different parts of the brain. One of the reasons behind this huge variability is that BOLD signal is not a calibrated measure; it is just a qualitative variation over a baseline (BOLD varies 1% ~ 5% from the baseline). BOLD signal depends on three other entities: cerebral blood flow (related to the regional metabolic demand of oxygen), cerebral blood volume (related to the amount of blood present in the brain) and oxygen consumption rate (Hoge, 2012; Blockley et al., 2013).

Furthermore BOLD is also dependent on multiple confounding physiological factors: from smoking and drinking habits, to caffeine intake, salad consumption, amount of exercise (see https://thewinnower.com/papers/concomitant-physiologic-changes-as-potential-confounds-for-bold-based-fmri-a-checklist for an exhaustive list of concomitant physiologic confounds for BOLD). It is however usual practice to accept the BOLD variability across and within subjects and, to partially compensate for these differences, the data is furthered filtered in time. Although intuitively one can imagine the temporal filtering like some sort of temporal smoothing, in practice there are physiological and technical reasons on why temporal filtering is necessary with fMRI BOLD data. To understand these reasons one must look at the spectrum of the BOLD signal across the literature (Figure 4).

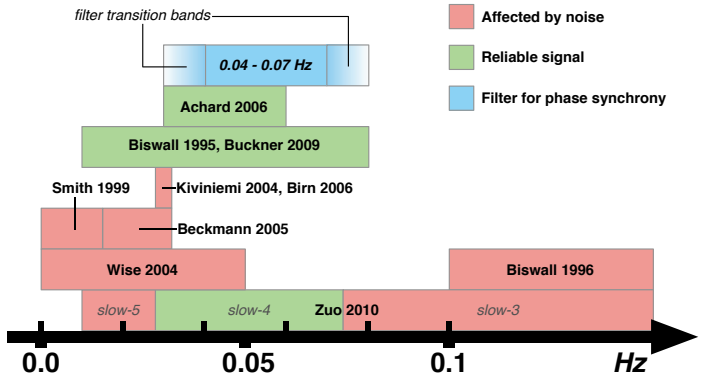

Figure 4. Frequency bands of BOLD signal. A summary of functional relevance of various frequency bands of the BOLD signal based on previous studies. Light red bars indicate frequency bands that have been observed to contain noise, green bars indicate frequency bands noted as functionally relevant, and the light blue bar indicates the narrow frequency band that was used in Study II in the current thesis.

As BOLD is a signal that depends on blood flow and oxygen concentration, two critical physiological processes are involved: cardiac and respiratory rate, with frequencies around 1–2 Hz and 0.3 Hz, respectively (Biswal et al., 1996). Since fMRI data is usually collected at a TR of 2 seconds (Nyquist frequency of 0.25 Hz), both respiratory and cardiac frequencies are out of band, causing aliasing in the highest frequency range of BOLD signal. Furthermore, spontaneous fluctuations in arterial carbon dioxide level affect the BOLD signal in the frequency range 0.0–0.05 Hz (Wise et al., 2004) and another noise component around 0.03 Hz is attributed to respiratory-related fluctuations when a slow TR is used (Beckmann et al., 2005; Birn et al., 2006). There are also technical reasons related to the stability of the magnetic field of the scanner: the so-called "low frequency drift" (Smith et al., 1999) affects the lowest end of the BOLD spectrum (0.0 – 0.015 Hz). Removing these sources of noise is important when computing the similarity between two time series from the same brain (see Functional Connectivity sub-section), since both time series are affected by the same correlated cardiac, respiratory and scanner-related noise. The usual practice is to band-pass filter the BOLD signal at 0.01–0.08 Hz (Biswal et al., 1995; Buckner et al., 2009; Zou et al., 2008), however sub-bands of the BOLD signal have been explored. Slow sub-bands relevant in electrophysiological DC and intracranial recordings (Penttonen and Buzsáki, 2003) are referred as: slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz). In Zuo et al. (2010) the slow-3 and slow-2 bands were identified in the white matter, mostly due to aliased respiratory and cardiac signals. Slow-4 and slow-5 bands were mainly mapped on the gray matter, with slow-4 being the most reliable sub-band. Similarly, a 0.03–0.06Hz band was also reported to give more stable results with graph theoretical tools (Achard et al., 2006). In Figure 4 a summary of these frequencies is plotted.

2.2.2 fMRI data collection and structure

As explained above each fMRI volume is collected in slices. Slices can be collected sequentially (usually in the feet to head direction) or in interleaved order for example first collecting odd numbered slices and then even slices. Interleaved order is preferred to minimize the effect of subject motion during the acquisition of a volume. After the data is collected, the resulting data structure is a four dimensional volume (with time being the fourth dimension), i.e. a collection of voxel time series covering the whole head. Tools such as SPM (http://www.fil.ion.ucl.ac.uk/spm/) and FSL (http://fsl.fmrib.ox.ac.uk/fsl/) are used to preprocess fMRI data for further analysis steps. In the next section I describe the preprocessing pipeline implemented by FSL which was used in the studies of this thesis (for a general reference on preprocessing steps, see Sarty, 2007).

2.2.3 Preprocessing – head motion correction

Subtle head motion during scanning can be due to involuntary head movement or as a consequence of breathing (Zeng et al., 2014). Motion is characterized as a translation along the three Cartesian axes (x y z) and rotation around each axes (in x y z order: pitch, roll, yaw). Motion correction estimates the best rigid translation and rotation between two consecutive volumes. This produces a time series of transformation matrices from which it is possible to generate motion parameters, estimates of translation and rotation (usually in millimeters for translation and radians for rotation). Head motion is one of the major concerns in fMRI literature especially when the similarity between two signals from the same brain is assessed. Previous studies have noted that due to motion artifacts, functional connectivity is distorted (Power et al., 2012): Similarity between neighboring voxels is increased (more short-distance connections) and similarity between faraway voxel is decreased (less long-distance connections). This is a cause of concern especially when studying population that have difficulties in keeping their head still such as children (Supekar et al., 2013).

2.2.4 Preprocessing – from subject space to standard space

After motion correction, since each individual's brain is anatomically different, we need a way to compare the brain activity of different subjects by matching same anatomical structures into a common standard reference brain. Although brain anatomy does not coincide with functions (similar functions can be located in anatomically different areas; Sabuncu et al., 2010), registration to a standard space by matching anatomy is considered the best approach. Registration is usually performed in two steps by firstly co-registering the subject's functional images to the structural one. Secondly, the individual anatomical brain structural image is co-registered with the standard reference brain template. The de facto standard template space is the Montreal Neurological Institute (MNI) 152 template, which is the average of 152 healthy participants' anatomical brain scans.

2.2.5 Preprocessing – increasing signal to noise ratio

The final part of preprocessing includes increasing the signal to noise ratio of BOLD time series by applying: i) spatial filtering – neighboring voxels get blurred together to increase functional similarity after co-registration and get rid of thermal noise in individual voxels; ii) temporal filtering – high pass filter to remove scanner drift (at frequencies < 0.01Hz) and low pass filtering to remove aliasing from heart beat and breathing. Further preprocessing steps include the regression of motion related parameters, and signals at deep white matter and ventricles (Power et al., 2014). When computing connectivity, often the global signal (average of all voxels) is regressed out. However, there is no consensus whether or not this should be done. Regressing global signal may reduce task effects (Van Dijk et al., 2010) and can systematically bias network comparisons (Gotts et al., 2013).

2.3 FMRI analysis – pairwise relationships between BOLD time series

In this section I describe "data driven" methods where, instead of comparing BOLD time series with an external model time series, pairs of BOLD time series are compared. Looking for a relationship between two time series often means looking for statistically significant similarity. For this purpose there are basically two approaches: 1) intersubject synchronization: comparison of two time series from the same areas of two different brains 2) functional connectivity: comparison of two time series from different areas from the same brain. Other between-brain approaches are also possible (Stephens et al., 2010).

2.3.1 Intersubject synchronization

The most popular way of computing intersubject synchronization is the intersubject correlation (ISC) method (Hasson et al., 2004; Kauppi et al., 2010). Briefly, ISC is the Pearson's correlation between BOLD signals for each brain voxel of all participants. To intuitively understand ISC, one can think that if we knew the hypothetical model of the activity in the selected area (e.g. in early visual cortex it would be high during visual stimuli and low in darkness), the standard general linear model (GLM) approach would identify a strong correlation (similarity) between the model and each subject time courses (Figure 5A). Although correlation is not a metric that satisfies the transitivity property (if A is highly correlated with B and B is highly correlated with C, there are cases for which A is not correlated with C) in practice with real data it is easy to intuitively simplify it in a sense that if two brain activity time series from two different individuals are similar to a model time series, *most likely* they are also similar between themselves. By looking at the similarity between subject pairs, it is then possible to bypass the model and – with permutation testing – claim that the haemodynamic response for the selected region is highly reliable during the processing of the stimuli (Figure 5B; for an exhaustive comparison see Pajula et al., 2012).

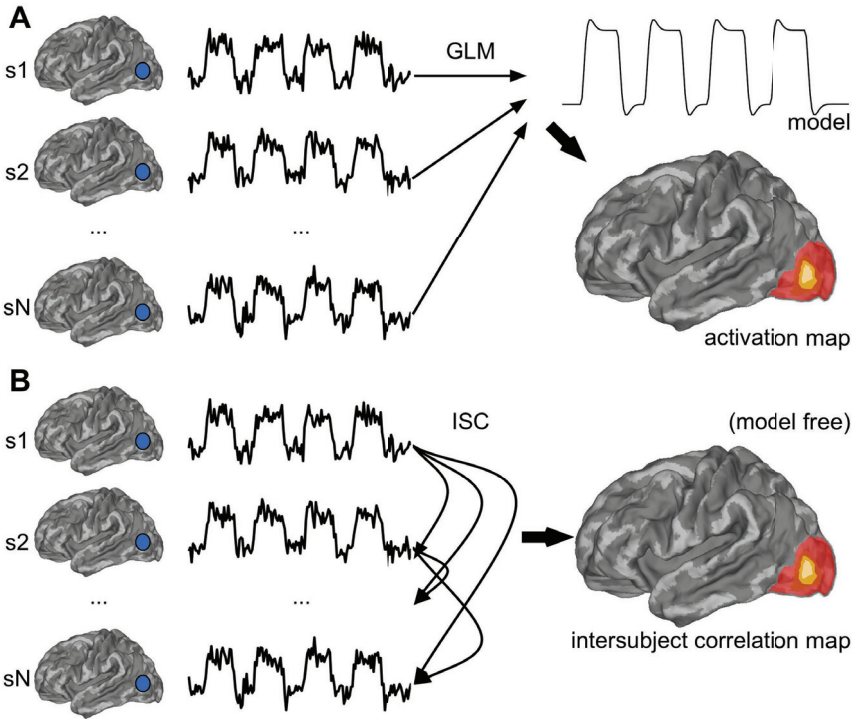

Figure 5. An intuitive explanation of intersubject correlation (ISC) compared to the general linear model (GLM) approach. A) When having a stimulus model, we can compute the similarity between each subject and the model with linear regression (GLM, first level analysis), and infer a group consistency map (second level analysis), which shows the goodness of fit of the model and the location of the voxels covarying with the model. B) With ISC however, the model is not known. If we still assume that each subject is similar to a hypothetical model, we can also test whether the subjects are all similar to each other by considering subjects pairs on which one's activity is the model for the other's. This leads to a similar group level map of reliability of the activations.

ISC has often been used at the group level, however by looking at the full variance between subject pairs of the ISC matrix, one can investigate whether the similarity between two subjects can be explained by a behavioral variable or if the similarity during one condition is higher than in another condition or – with clinical applications – if the similarity within one group of subjects is higher than the similarity of another group of subjects. Since ISC is performed for a single voxel, by repeating the analysis for all voxels we obtain a statistical volume that shows which areas have strong ISC.

2.3.2 Functional connectivity

Functional connectivity (FC) is usually computed as the Pearson's correlation between two activity time series from two separate regions of the same brain, although a plethora of methods exist (Smith et al., 2011). For strong values of correlation we can then say that the two areas functionally connected, i.e. the two time series are oscillating in sync. Synchronous oscillations of brain time series are usually interpreted as brain areas "talking" to each other. Animal

studies confirm this idea by combining BOLD with other imaging techniques such as local field potentials in non-human primates (Schölvinck et al., 2010; L. Wang et al., 2012). Furthermore, modeling studies using simulated data, also show that when voxels are distributed over a structural network matching for example the network obtained with DTI, the spontaneous behavior of voxels give rise to the similar data as seen at resting state (Cabral et al., 2011). Functional connectivity has proven to be a useful tool in quantifying anatomical connectivity in the healthy and clinical populations (Sporns, 2014; Stam, 2014).

2.4 Time-varying ISC and FC: time windowed correlations

Recently, a growing number of scientists have been interested towards adding the temporal dimension to the proposed data driven methods. While on average we can claim that two subjects show strong ISC or that two specific brain areas are strongly connected, we might also want to investigate whether the level of ISC or FC could change in time for example while being modulated by the stimulus.

A simple way for adding time to the analysis is to consider the time series over a smaller temporal sliding window. While ideally one can think that the average correlation within sliding windows will produce the total correlations of the two non-windowed signals, in practice this is only valid for stationary systems. The brain, being a complex system, is far from producing stationary or ergodic behavior (Hutchison et al., 2013). What this implies is that looking at connectivity over time windows introduces information that is not available over longer time scales. The consequence of this is that the selection of the duration of the window is important. The longer the time window, the more the value of correlation will resemble the one of the static correlation. With shorter time windows, more spurious results are obtained (Leonardi and Van De Ville, 2015), making it complicated to evaluate dynamic ISC or FC while processing naturalistic stimuli.

2.5 Instantaneous phase synchronization

Phase synchronization (PS) was initially introduced in physics for modeling the interaction between two weakly coupled oscillators (Rosenblum et al., 1996), by separating the instantaneous amplitude and phase and considering only the phase component. This approach is one of the bases expansions, in which a one-dimensional signal is expanded into a multi dimensional signal to extract further properties. A filter bank for example separates a signal into sub-frequencies; wavelet transform and Gabor expansion are other examples of signal expansion. PS uses the properties of the analytic signal to firstly convert a real signal into a complex signal with the same information. The analytic signal of a real signal is obtained by rearranging the frequency content of the original signal using the Hilbert transform, which keeps only the positive side of the frequency spectrum. Then, by using the Euler's equation, the complex

signal is rewritten as the product of amplitude and phase signals (equation 3 in Study II). However this comes with a trade-off: to have meaningful amplitude and phase signals, the original signal has to be narrow-band. This is to satisfy the Bedrosian's theorem (Bedrosian, 1962), for which the Fourier transforms of the two signals have separate supports (i.e. amplitude and phase signals are changing at different frequencies).

In the following, I try to make it intuitive why only the phase part of the analytic signal is considered. When doing sliding window correlation between two signals, the mean and variance within that window are scaled before computing the product between the two windowed signals. The scaled mean and variance can be thought as a slow amplification factor over the signal that is discarded in the short scales of the temporal window, i.e. equivalent to discarding the amplitude of the analytic signal. Finally, as the bandwidth of BOLD signal not affected by noise is narrow (see previous sections), BOLD is a perfect candidate for applying PS. The portion of useful signal is in the frequency range of 0.04–0.07 Hz, equivalent to the slow-4 band minus the 0.03 Hz critical frequency (see Figure 4).

The novel PS metrics proposed in Study II are: i) Intersubject Phase Synchronization – a measure equivalent to sliding window ISC; ii) Seed Based Phase Synchronization – a measure equivalent to correlation based functional connectivity over a sliding window; iii) Intersubject Seed Based Phase Synchronization: a measure with no correlation equivalent, it requires that all subjects have dynamic connectivity and activity in synchrony. The latter measure, by ensuring that all pairs of regions are synchronized, is computing the extrinsic dynamic connectivity rather than revealing intrinsic dynamic processes (see description of Study II).

2.6 Graph theory and neuroscience

Graph theoretical measures can be applied at the level of nodes and links (micro-level), at the global level of the whole network (macro-level) and at the intermediate level of subnetworks, also known as modules or communities (mesoscopic level, see Figure 6 for a simple example). For a general reference for this section, see Newman (2003), Rubinov and Sporns (2010).

In this thesis, as a micro level feature, I used node strength as a measure to quantify the importance (or "centrality") of the node in the network. Central nodes are usually called hubs, and – as in colloquial language – they can be thought as pivotal nodes in the network. Removing the most important hubs usually causes the network to disconnect. The node degree (node strength for the weighted case) is an estimate of node centrality, obtained by computing the sum of the links attached to a node (or sum of the weights for weighted case). On the other hand, use of macro level network properties is a way to characterize the whole network with a single meaningful number (e.g. the total number of links or the average path length between each pairs of node). For brain, these properties are useful when major reorganization takes place for example in

schizophrenia, Alzheimer's disease (Bullmore and Sporns, 2012) or in comatose patients (Achard et al., 2012).

However, the functional organization of a network may not be visible at the micro or macro level. Rather, it becomes evident at the mesoscopic level of subnetworks that can be inferred from network structure (Fortunato and Castellano, 2007).

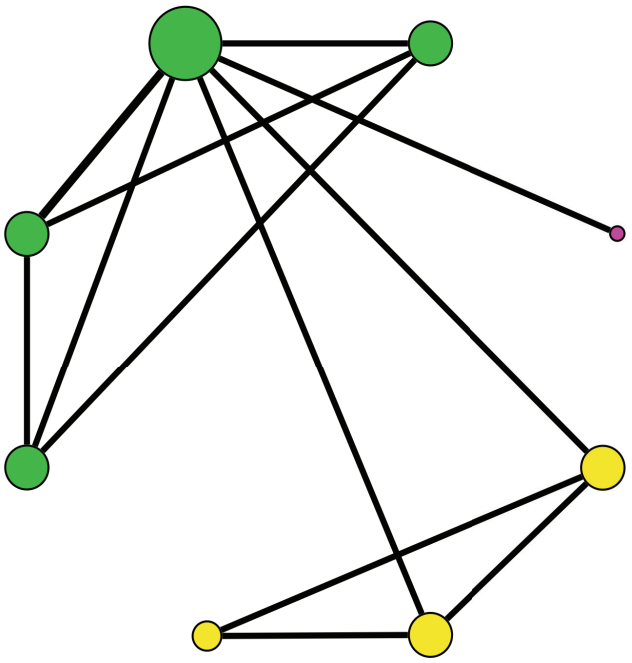

Figure 6. A simple visualization of micro and mesoscopic network properties: the size of each node is scaled with its node degree (the sum of the number of links attached; node strength for the weighted network case). Nodes who are "all friends with each other" form a cohesive community (three communities in green, yellow and purple), since the number of links between them is higher than the number of links going outside from them.

Although multiple methods exist to compute the modules of a network, I adopted the Louvain method that maximizes the modularity of the partitions (i.e. finds the partition for which most of the links in the network are within the same modules and not between modules). Quantifying subnetworks statistically is, however, a challenge (Alexander-Bloch et al., 2012). In this thesis I adopted Scaled Inclusivity (Moussa et al., 2012, p. 20; Steen et al., 2011) as a measure of intersubject similarity of a subnetwork. Scaled inclusivity (SI) is calculated for each node after computing the modules. Intuitively: if the node considered belongs to a module that is spatially overlapping (i.e. made of almost the same nodes) in both subjects, then the value of SI is high for that pair of subjects and that node. Using the median across a subnetwork, a mesoscopic-level similarity between subject pairs can be computed.

2.7 Behavioral and diagnostic tools

In the presented studies a selection of tools were used to assess the content of the stimuli and the participants.

2.7.1 Dynamic rating tool

This dynamic rating tool was developed for Study I, and later became quite useful in other studies assessing a time-varying behavioral variable (Nummenmaa et al., 2014b). The tool is developed in Adobe's Flash Action Script, a programming language for building interactive content for the web. The tool displays a video on a webpage and with the mouse allows the rating of one-dimensional variable. In our studies subjects rated emotional arousal and valence. Mouse movements are sampled every 200ms (5 Hz). Although higher sampling rates would have been possible, I took into account the fact that different computers might lead to different performance if the requirements were too strict. Preliminary testing indicated that 5 Hz sampling rate gave good performance in multiple machines, browsers and operating systems. The final data consist of a time series with values from 0 to 1. Time series were always z-scored.

2.7.2 Emotional empathy and tests for autism

In Study I, the Measure of Emotional Empathy questionnaire (Mehrabian and Epstein, 1972) was used. In study IV autism quotient (AQ, (Baron-Cohen et al., 2001), Autism Diagnostic Interview Revised (ADI-R, (Lord et al., 1994) and Autism Diagnostic Observation Schedule (ADOS, (Lord et al., 1989) were used. While AQ is a screening test, ADI-R and ADOS have diagnostic value.

2.7.3 Eye-tracking

Eye movements consist of fixations (short stops of the eyes on a target) and saccades (quick simultaneous movement of both eyes). While the eye-tracking technique is not new per se, only in recent years it has been used to track eye movements during dynamic videos to compare fixations across healthy individuals (H. X. Wang et al., 2012) and ASD populations (Hasson et al., 2009). Study III proposes the measure of eyeISC, i.e. a time-varying intersubject correlation measure of reliability of the fixation maps during movie watching. This provides a behavioral annotation of the similarity of gazing patterns across subjects, computed over temporal windows equal to one TR.

2.8 Intersubject analysis framework and statistical testing

Finally, to explore the full information stored in the intersubject correlation matrix, I devised the intersubject analysis framework (ISA, Figure 7) in which the similarity between two subjects' behavioral score is compared with the pair's similarity of a brain variable such as a voxel time series, or the similarity of connectivity structure with scaled inclusivity. Mathematically, this is equiva-

lent to comparing two similarity matrices, and the significance of their correlation is tested with the Mantel test using permutations (Mantel, 1967). A similar approach is also adopted in genome wide association studies (GWAS) to test if subjects with similarities of phenotypic or behavioral traits are explained by similarity in the genes (Zapala and Schork, 2006). In a different context, the framework is also known in other form as the multi-voxel pattern analysis (MVPA) technique Representation Similarity Analysis (RSA, Kriegeskorte et al., 2008) although in RSA the similarity is computed between stimuli, while here the similarity is between subjects: the intersubject pattern obtained for behavioral scores is matched to the intersubject pattern of brain activity or network similarities. In the present studies I used the similarity between continuous self-reports of valence (Study I) and the similarity between autism scores, by taking each sub-score as part of a vector (Study IV). Another possible test is to look for group differences, by comparing if one group (or condition) has higher ISC values than the other (Salmi2013, Kauppi2014), this was used in Study III and study IV. Finally, it is also possible to look at the significance of ISC without comparing groups or with a model, as implemented by the ISC-toolbox (Kauppi et al., 2014) and this was used in all studies of this thesis.

All methods described here are relatively new and in most of the cases required novel approaches for statistical testing. Since all the measures described might not follow known parametric distributions, permutation tests become handy to estimate the level of significance and correct for multiple comparisons. With permutation testing it is possible to generate a distribution of surrogate results (a null distribution) obtained from a randomized version of the original data by reshuffling the correct group labels or time-points order (Good and Wang, 2005). For the Mantel test, this means swapping the rows and columns of the similarity matrix so that subjects' order is shuffled. This is repeated some thousands of times, and each time a surrogate correlation value is computed. By comparing the original correlation value (without shuffling) with the thousands surrogate values, a frequency of significance (a p value) can be obtained. For example, if the real correlation value is bigger than the 95^{th} percentile of the surrogate values, then it corresponds to a $p < 0.05$. The same is done when testing time series, however time points can be truly shuffled only if there is no autocorrelation between them (i.e. a Gaussian signal). In practice, all sampled signals are auto-correlated, which led to the development of techniques to generate shuffled time series that retain similar autocorrelation, for example by generating surrogate time series based on the frequency spectrum of the time series (Dolan and Spano, 2001) or based on shuffling the original signal in the temporal domain by keeping contiguous blocks of data (Politis and Romano, 1992). Finally, when considering many variables at once (voxels, network nodes, network links), it is necessary to control for multiple comparisons. The distribution of the estimated p-values can be corrected using the false discovery rate procedures (FDR) such as the one by Benjamini and Hochberg (Benjamini and Hochberg, 1995), or family-wise error rate approaches such as the maximum statistics (Nichols and Hayasaka, 2003). When

it comes to large networks, the number of links grows quadratically with the number of nodes, which makes it challenging to use the FDR approach. Alternatives such as the Network-based Statistics (Zalesky et al., 2010; Han et al., 2013) provide the equivalent of spatial cluster correction in the domains of the network rather than on voxels.

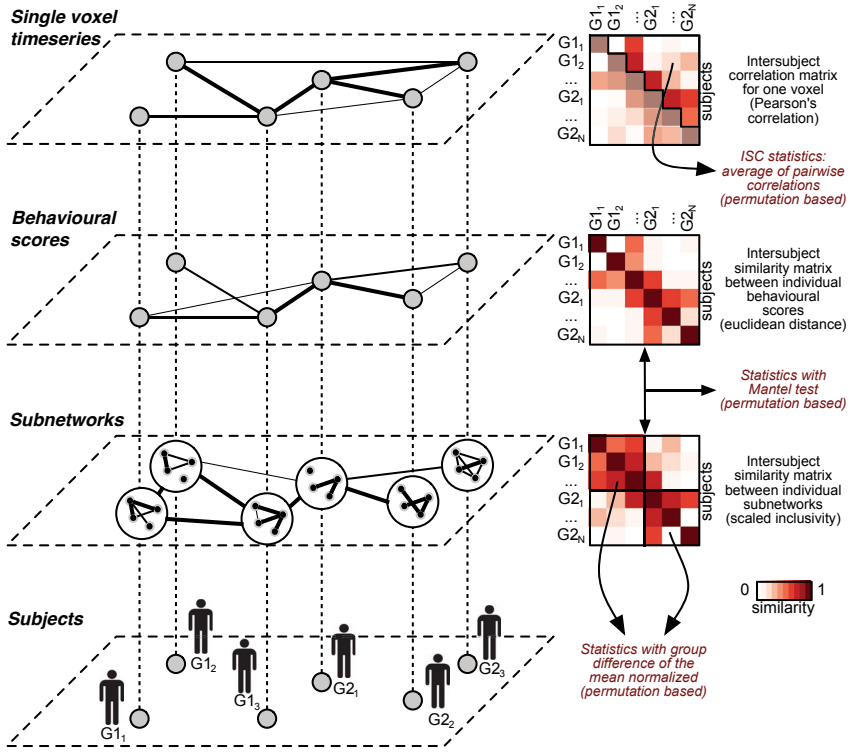

Figure 7. A schematic representation of the intersubject analysis framework. For two groups of subjects (bottom layer, groups G1 and G2), we can compute the similarity between each subject pair by using functional brain data at the level of a single voxel ("Single voxel time-series" layer), using behavioral scores ("Behavioral scores" layer) or using more complex modeling methods (e.g. similarity at the level of subnetworks). These similarity layers are depicted as networks and as adjacency matrices also known, in this case, as intersubject similarity matrices. Three types of statistical tests can then be run (marked in dark red in the figure): a group difference within a layer, in which the within groups values of the adjacency matrix are compared (bottom adjacency matrix, where the group comparison tests whether the within G1 group similarity is higher than the within G2 group similarity). The second test is the Mantel test, in which two similarity matrices are compared with each other by correlating the corresponding values of the top off-diagonal triangle. In the latter case, also the between group similarity values are used making the Mantel approach more strict. The third test is the whole-group intersubject correlation, as the significant level of average pairwise similarity for a single voxel time-series as implemented by the ISC toolbox.

3. Goals of the current research

The aim of these studies is to examine the full intersubject variance of brain responses from a group of participants, in order to investigate the similarity of brain activity and connectivity during social and emotional naturalistic stimulation. Overall goal is to apply the intersubject analysis framework at the level of voxels (intersubject correlation) and at the level of subnetworks (scaled inclusivity) and to further extend it in the temporal dimension to compute time-varying similarity between subjects and between brain regions. The studies further tested the clinical application of such methods to address the wide spectrum of autism. By evaluating each subject in relation to the others, rather than labeling them into one single clinical group, the proposed methods try to highlight what is common across high functioning individuals with autism as well as healthy controls.

Study I tested whether emotions trigger time-locked activity in the viewers' brains as a possible mechanism to facilitate interpersonal understanding and empathy.

Study II aimed at testing phase synchronization and its inherent instantaneous properties as a viable tool for computing group level similarity between time series of haemodynamic activity.

Study III aimed at testing whether a perspective-taking task is reflected as synchronized haemodynamic activity between subjects taking the same perspective.

Study IV tested whether high functioning individuals with autism spectrum disorder with similar symptoms share similar connectivity patterns. The aim of the study was to use graph theoretical tools at level of subnetworks to overcome the known mixture of hypo- and hyper-connectivity at the single node and link level in connectivity literature of ASD.

4. Summaries of the studies

4.1 Study I: Emotions promote social interaction by synchronizing brain activity across individuals.

4.1.1 Aim of the study

Observing others in an emotional state – such as pain, disgust or pleasure – elicits a corresponding feeling, physiological activity and neuronal activations. The aim of this study was to test whether emotions trigger time-locked activity in the viewers' brain as a possible mechanism to facilitate interpersonal understanding and empathy.

4.1.2 Materials and methods

Sixteen healthy volunteers watched 16 short pleasant, unpleasant and neutral film clips while their hemodynamic brain activity was recorded with fMRI. After the scanning, the participants reported the perceived pleasantness (valence) and arousal. By moving a mouse (see Figure 8) they indicated their moment-to-moment experiences of valence (pleasantness–unpleasantness) and arousal.

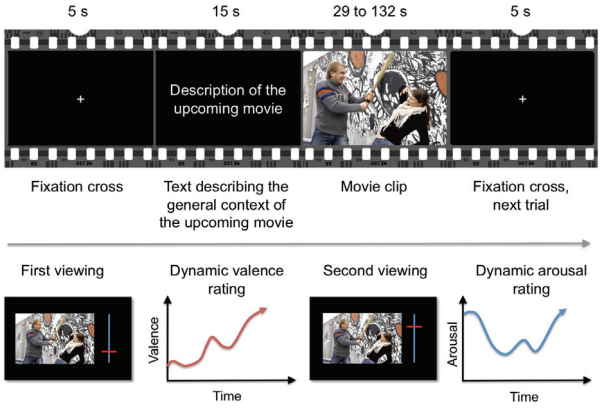

Figure 8. Design for the fMRI experiment and behavioral task outside the scanner. Short movie clips contained pleasant, unpleasant, and neutral events. Each clip was preceded by a 5-s presentation of a fixation cross and was followed by a 15-s presentation of text that provided a neutral context for the following video. For the behavioral task, participants watched the clips twice and rated valence and arousal dimensions with a web-based tool.

After standard preprocessing fMRI data was analyzed in four different ways. Firstly, group average ISC was computed across the whole experiment to identify areas significantly intersubject-correlated. Individual average ISC maps were also computed (obtained as the average similarity of one individual versus the rest) and were then voxelwise regressed with individual scores of Measure of Emotional Empathy questionnaire. Secondly, we calculated moment-to-moment group ISC over a temporal sliding window of 10 samples (equivalent to 17 seconds) resulting in voxelwise time series of group ISC that were regressed with the group average valence and arousal ratings time series. Thirdly, to test whether the resulting regions modulated by valence and arousal belong to dissociated subnetworks, we computed the subnetwork-level ISC time series (average ISC across a subnetwork) within the six functional brain subnetworks: visual, sensorimotor, auditory, default-mode, dorsal attention and executive control. Subnetworks were identified with seed voxel correlation in a set of seeds with highest ISC-by-arousal and ISC-by-valence. We then identified how the ISC dynamic of each subnetwork was modulated by valence and arousal. Finally we used the intersubject analysis framework (in the manuscript described as representational similarity analysis – RSA) to test if the similarity between individual ratings was corresponding to the similarity of BOLD time series.

4.1.3 Results

Behavioral ratings confirmed that the clips conveyed strong emotional content and were consistent across subjects (Figure 9). Group average ISC analysis across the whole experiment showed significant synchronization in occipito-parietal visual cortices as well as in temporal and frontal areas and in affective processing regions such as amygdala and anterior insula (Figure 10).

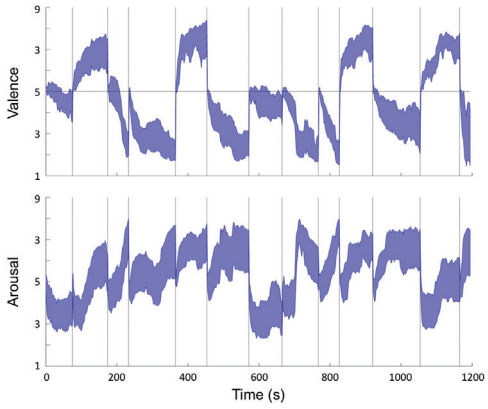

Figure 9. Time series of self-reported valence and arousal scores. The figure shows the 95% confidence interval for the valence (Upper) and arousal (Lower) ratings across all 16 subjects. Vertical lines denote breaks between movie clips. In the valence plot, the horizontal line at 5 denotes neutral valence. Note that during the functional MRI experiment there were 20-s breaks between the film clips.

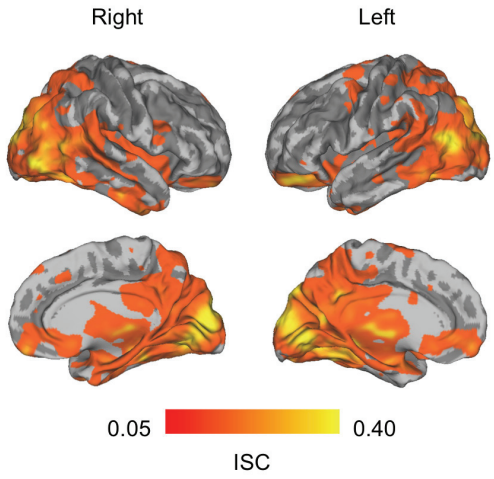

Figure 10. Brain regions with statistically significant (P < 0.05, FDR corrected) group-level ISCs during viewing of all film clips. Significant ISC was found in visual areas as well as posterior and inferior temporal, insula and subcortical structures (e.g. amygdala).

When comparing the temporal dynamics of ISC in relationship to valence and arousal (Figure 11), a decrease of valence was associated with increased ISC in emotional processing areas (ventral striatum, medial prefrontal cortex, anterior cingulate) as well as in areas belonging to the default-mode subnetwork (precuneus, ventro-medial prefrontal cortex and temporo-parietal junction). Increasing arousal was associated with increased ISC in visual and somatosensory regions as well part of the dorsal attention network (intra parietal sulcus, frontal eye field).

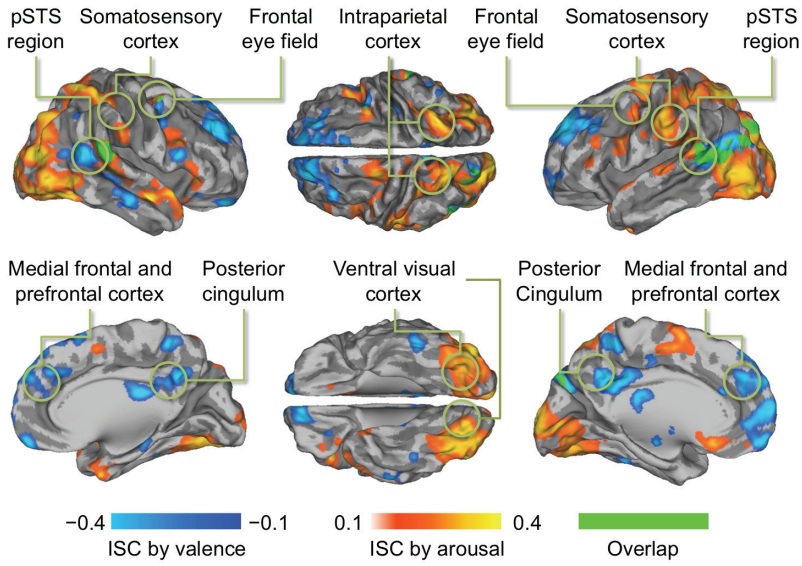

Figure 11. Brain regions where dynamic ISC was statistically significantly correlated (P < 0.05, FDR corrected) with self-reported valence (blue to light blue) and arousal (orange to yellow) scores.

When looking at how the results coincide with previously defined functional networks, we found that ISC-by-valence was overlapping with the calculated default mode seed map while ISC-by-arousal overlapped with dorsal attention and visual subnetworks (Figure 12).

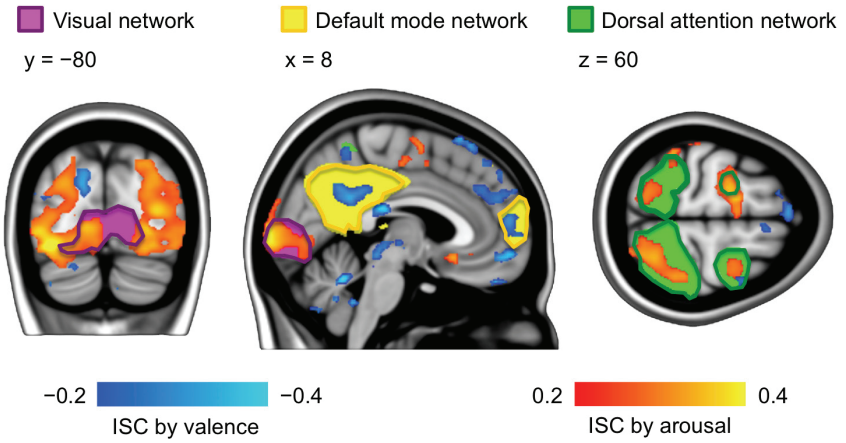

Figure 12. Valence modulates ISC in the default-mode network (yellow) and arousal in the visual network (violet) and dorsal attention network (green). Brain regions where ISC was statistically significantly correlated with self-reported valence (blue to turquoise) and arousal (red to yellow) scores during viewing of film clips ($P < 0.05$, FDR corrected).

Figure 13 depicts those brain areas where intersubject similarity of BOLD signal was significantly correlated with similarity of valence evaluations.

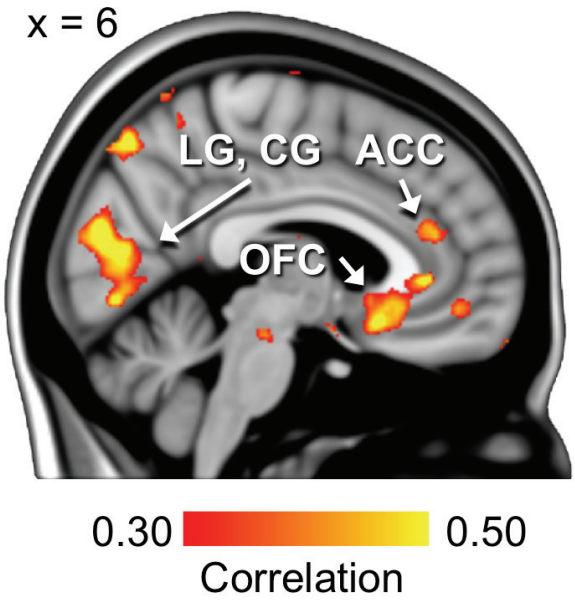

Figure 13. Brain regions where the intersubject similarity of blood oxygen level-dependent (BOLD) time courses is significantly correlated with the intersubject similarity of subjectively reported valence time courses. ACC, anterior cingulate cortex; CG, calcarine gyrus; LG, lingual gyrus; OFC, orbitofrontal cortex.

Finally level of emotional empathy was associated with individual average ISC score in posterior temporal gyrus, i.e. activity in this region was more similar for participants with higher empathy scores

4.1.4 Conclusions

The results showed that when watching strong emotional scenes, brain activity synchronization across subjects goes well beyond sensory cortices. We found distinct and separate mechanism for valence and arousal: arousal was strongly related to time-varying ISC in attention circuits and somatosensory cortices. Valence had a negative association with ISC, correlating with the dynamics of the default mode network. Finally, valence was also correlating with higher level of ISC in frontal areas as identified by the group analysis as well as when considering individual differences in the ratings. These results support the hypothesis that synchronous brain activity across individuals might function as the pivotal mechanism in understanding other's emotional states and possibly promote social interaction.

4.2 Study II: Functional magnetic resonance imaging phase synchronization as a measure of dynamic functional connectivity

4.2.1 Aim of the study

In the analysis of time series, there is a trade-off between temporal resolution and signal to noise ratio: the more time points we have (longer time window, lower temporal resolution) the better we can estimate properties of the signal (e.g. mean, variance, frequency spectrum). With usual fMRI experimental paradigms like block or event related design, properties of the BOLD signal can be averaged over the whole block and over multiple repetitions, however with highly complex naturalistic stimuli, there are unique events that are not repeated. The aim of this study was to develop an instantaneous measure of synchronization between subjects (intersubject phase synchronization) and within a subject (seed based phase synchronization) and to compare it with the sliding window correlation approach.

4.2.2 Materials and methods

We proposed three metrics: intersubject phase synchronization (IPS), seed-based phase synchronization (SBPS), intersubject seed based phase synchronization (ISBPS, see Figure 14 for a graphical representation). IPS was compared with the sliding window intersubject correlation, SBPS was compared with sliding window functional connectivity with Pearson's correlation, the third measure does not have a correlation equivalent and it can be interpreted as a connectivity between and within multiple brains, to identify synchronous connectivity dynamics that are intersubject correlated. To compare the results we used a previously published dataset of 12 healthy subjects watching an edited version of the Finnish feature film "The Match Factory Girl" (Lahnakoski et al., 2012b). IPS was compared with sliding window ISC across the whole brain, while for SBPS we used a set of 264 regions of interests (ROIs) defined in Power et al (2011). Visualization of the dynamic connectivity results were done for two ROIs in the right visual cortex: V1/V2 (ROI #140) and MT/V5+ (ROI #161). Details about the method and the required band-pass filter are explained in chapter 2.5. We also tested the envelope of the analytic signal to assess whether there was significant information synchronous across subjects using sliding window correlation.

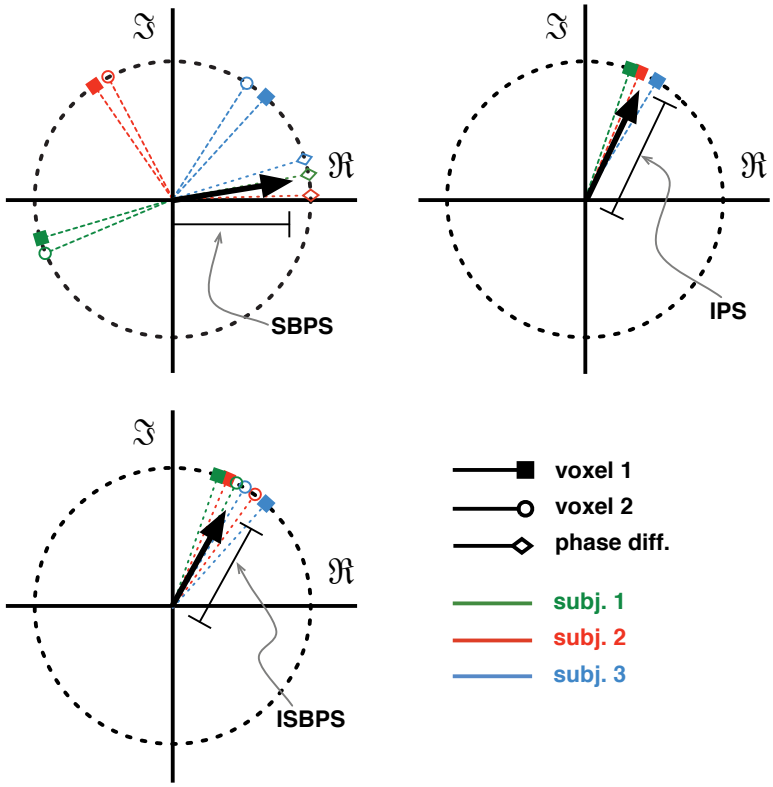

Figure 14. Functional magnetic resonance imaging phase synchronization metrics. Each panel is a temporal snapshot for a single time point. (1) Seed-based phase synchronization (SBPS): for each subject the instantaneous phase difference between two regions of interest (ROI) time series is considered (diamonds), the length of the resulting vector (in black) shows the level of synchronization over the group. (2) Intersubject phase synchronization (IPS): only one ROI is considered, when all subjects have almost the same phase at the same time, the resulting vector length will be closer to unity. (3) Intersubject seed-based phase synchronization (ISBPS): a combination of the two previous metrics where two regions have to be in synchrony within a subject's brain and with other subjects.

4.2.3 Results

When comparing the average of IPS voxelwise time series with ISC across the total length of time points, the two maps were highly similar (Figure 15, A). When comparing the IPS time series with ISC sliding window time series, the greatest similarity was observer for a window of length around 8–10 volumes (Figure 15 B & C). Figure 15 D shows across all voxels the comparisons between different sliding window sizes. When the window is too small, correlation values are getting noisy and produce artifacts (there is mismatch between the lowest frequencies in the signal and the length of the window). For windows longer than 10 volumes, we tend to have more significant results but we lose the temporal resolution. Instantaneous IPS is then proving to be valuable in studying dynamic events in smaller scales than 12 volumes sliding windows. The envelope of the analytic signal did not provide significant information except for early visual cortices (not shown).

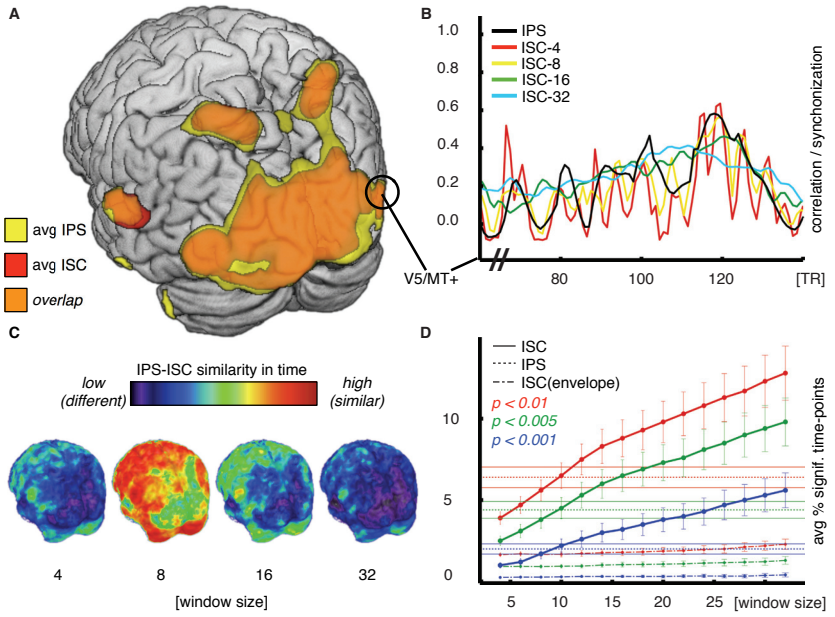

Figure 15. Intersubject correlation (ISC) and intersubject phase synchronization. (A) Maps, computed over the whole time series ($p < 0.01$, FDR corrected), of brain areas showing significant averaged IPS (yellow) and areas showing significant ISC (red); orange color for overlapping areas. (B) Time courses of IPS (black) and ISC calculated over sliding windows of different sizes from area V5/MT+. ISC over short sliding window (red curve, window size: four samples) shows computational bias as evidenced by rapid and strong fluctuation in the time course. ISC time series over longer sliding windows, although being more stable, are missing the faster temporal changes identified by IPS. (C) Similarity maps between IPS and sliding window ISC time series for four different temporal windows. When using a sliding window of 8 time points, dynamic ISC is the closest to IPS. Differences are located in sensory areas processing faster signal changes that IPS can track unlike time-windowed ISC. (D) Average percentages of significant time points with error bars for IPS (horizontal dotted lines) at three levels of significance and ISC with multiple time windows (continuous curves). ISC with multiple time windows calculated using the instantaneous amplitude envelope information is plotted with the dash-dotted curves.

When considering dynamic functional connectivity, the number of signals involved is now doubled (two time series per each subject). This is easily seen in the higher variability of the dynamic connectivity time series for the two selected ROIs (Figure 16 A). When comparing all the possible links between ROIs, sliding window correlation was able to match the average level of significance of SBPS only for windows bigger than 18–20 volumes. (Figure 16 B) Finally when comparing ISBPS with SBPS, requiring the synchrony of both ROIs results in a more strict dynamic connectivity time series possibly dissociating intrinsic dynamic processes from extrinsic ones. (Figure 16 C)

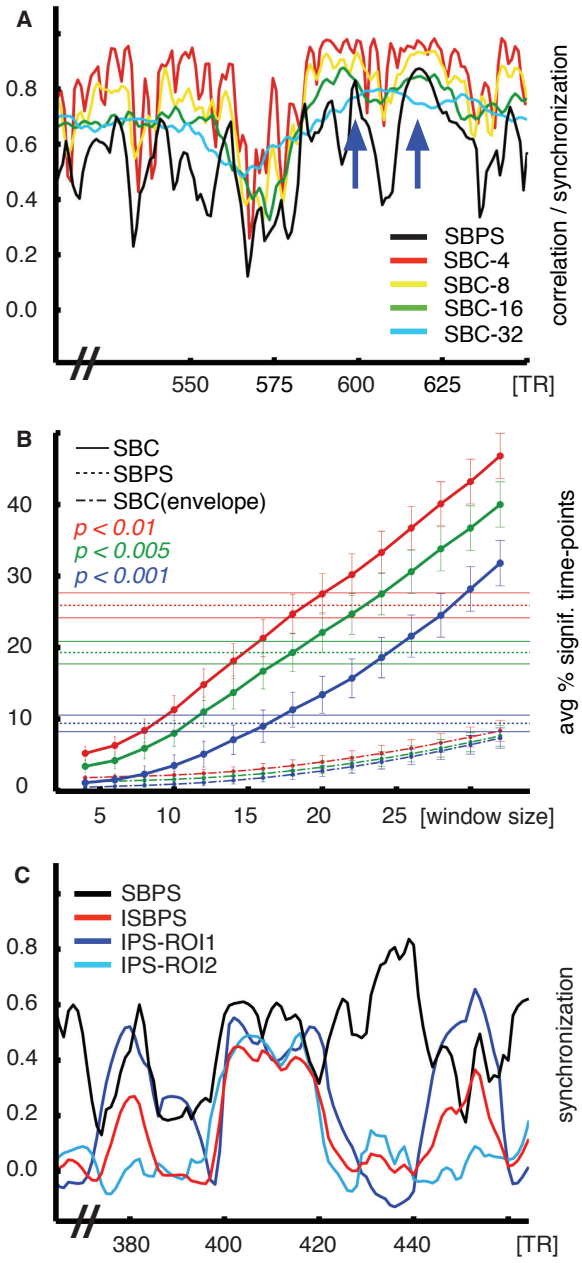

Figure 16. Dynamic functional connectivity between two ROIs with PS and seed-based correlation (SBC). A) SBPS (in black) and SBC calculated over multiple sliding windows between two ROIs. The blue arrows indicate peaks at 600 and 625 that corresponded to close-up scenes with movement (vs. large-angle panoramic scenes in the middle) that the SBPS method can differentiate in contrast to SBC when using longer time windows. (B) Average number of significant time points with error bars for SBPS (horizontal dotted lines), SBC using multiple time windows (continuous curves), and SBC with multiple time windows performed over the instantaneous envelope (dash-dotted curves). Comparable amount of significant time points is reached for SBC over windows of at least 16 samples, sacrificing the fast temporal dynamics identified with PS. (C) Comparison between ISBPS (red) and SBPS (black) along with the IPS curves for the two regions (blue and light blue). ISBPS is more conservative than SBPS since both ROIs must manifest intersubject synchronization.

4.2.4 Conclusions

The results showed how PS can reliably improve dynamic synchronization measures for the BOLD signal. The resulting synchronization time series can then be compared with external regressor as was done in Study I and this was successfully used in following publications to examine action simulation (Nummenmaa et al., 2014c) and to study the whole brain dynamic connectivity during emotional stimulation (Nummenmaa et al., 2014b). There are two inherent limitations of the method: i) the trade off of using a sub-band of the BOLD signal, although the considered part of the frequency spectrum has previously been shown to be the most reliable one. ii) The proposed measures are group level measure: Although PS has also been used in a single subject first level analysis (Kitzbichler et al., 2009), the lack of statistical power required temporal average, i.e. losing the added value of instantaneous information. Finally the removal of the signal envelope did not seem to remove valuable information reliable across subjects, however future studies should explore the envelope of the analytic signal as a possible marker of individual behavior and task performance.

4.3 Study III: Synchronous brain activity across individuals underlies shared psychological perspectives

4.3.1 Aim of the study

Mental states are supposed to be reflected in the brain as consistent patterns, "representations" in multiple brain regions. However it is not know if mental states tend to be more similar across subjects when, for example, taking the same mental perspective during a task. Here we hypothesized that while watching the same dynamic stimulus, similar psychological perspectives would be reflected as similar temporal activations, i.e. as increased intersubject correlations.

4.3.2 Materials and methods

Two datasets with similar design were collected (experiment 1: 20 subjects, replication experiment 2: 13 subjects). Participants watched a 10-minutes clip from an American TV series ('Desperate Housewives', Season 1, Episode 15, Cherry Alley Productions, 2005) in two different perspectives introduced by a background written story: a social perspective by taking the point of view of a police detective and a non-social perspective by taking the point of view of an interior/exterior decorator. Eye tracking was performed outside the fMRI scanner for experiment 1 and during fMRI data collection for experiment 2. Intersubject correlation of eye movements (eyeISC) was performed by correlating the spatial fixation heat maps derived over two seconds sliding windows (matched with the TR of the experiment). Average eyeISC values for the two experiments were compared to assess similarity of the spatial fixation pattern across the two experiments. Mean saccades amplitudes and fixations were also compared between perspectives. Furthermore, subjects also answered a questionnaire on the difficulty of the task, attention towards perspective-relevant and irrelevant content and what was important in the stimulus for the completion of the task. A free form answer was also given regarding how they performed the task and which features from the stimulus they found important.

The fMRI data was analyzed with the ISA framework: firstly ISC matrix between all runs was computed and permutation tests were used to find significant differences in the strength of ISC across perspectives, by using the ZPF sum statistics (the sum of Fisher-z-transformed correlations across all pairs) as implemented by the ISC toolbox (Kauppi et al., 2014). Then, mantel test was run to identify those brain areas that were consistent within the two perspectives but reliably different across perspectives. A further analysis was performed on the ISC coefficients using k-neighbor classification to separate intersubject voxel activity between the two cases (Figure 17). A similar classifier was also used to assess whether gaze patterns alone were predictive of the perspectives of the participants.

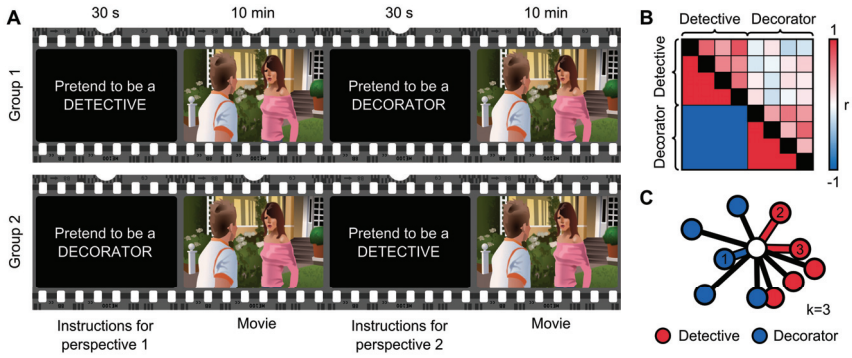

Figure 17. Experimental design and analyses. A: Participants watched the same movie clip twice from social (detective) and non-social (interior decorator) perspectives, with the starting perspective counterbalanced across participants. B: Mantel test was used to compare the pairwise ISC values (upper triangle entries) with a correlation matrix template (lower triangle entries) where ISC in same perspective pairs (red) was higher than different-perspective pairs (blue). C: Subjects were classified using a k-nearest-neighbors classifier according to the labels of the training subjects (detective–red, decorator–blue) with whom their ISC was highest. In the visualization the proximity between two dots reflects the strength of the ISC between those subjects. The nearest three neighbors are indexed according to their proximity to the current subject, and the links are highlighted with the color corresponding to their class. For k=3 the current subject (white dot) would be classified as a detective because two of the three nearest neighbors (neighbors 2 and 3) are detectives.

4.3.3 Results

Participants reported to pay more attention to task-relevant features in both conditions and both tasks were perceived as equally difficult (Figure 18). Freeform reports indicated that subjects were behaving according to the task: during the Detective perspective they were focusing on facial expressions of the characters while during Decorator perspective were focusing on the background and furniture in the stimulus.

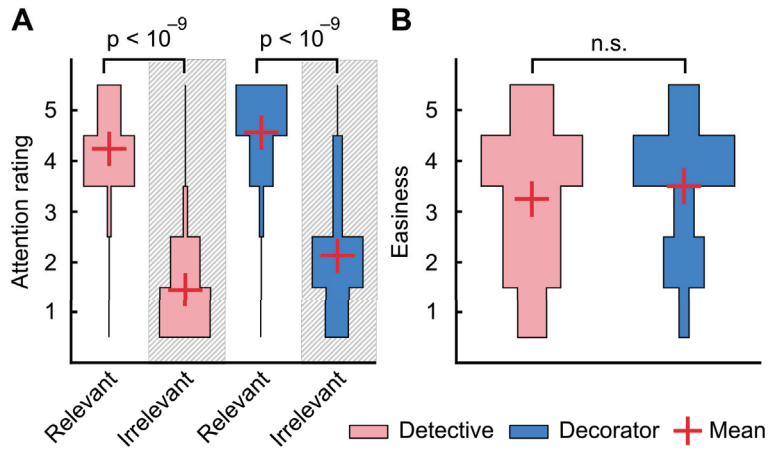

Figure 18. Behavioral results. A: Distributions of ratings across subject of their attention (on scale 1–5) to perspective-relevant and irrelevant items. B: Subjective evaluations of the difficulty of the tasks on a scale from 1 (very difficult) to 5 (very easy). Detective perspective is indicated by pink and decorator perspective with light blue color. The red crosses indicate the mean of the ratings across subjects.

In accordance to the questionnaires, fixation maps (Figure 19 A) showed that in Detective perspective subjects focused mainly towards the center of the image where actors were usually shown, whereas in Decorator perspective they mainly focused on the background. Participants also made longer saccades and shorter fixations during Decorator perspective (Figure 19 B). EyeISC was stronger in the Detective perspective throughout the whole stimulus, except during the opening credits. Mean eyeISC were basically the same inside and outside the scanner (Figure 19 D and E).

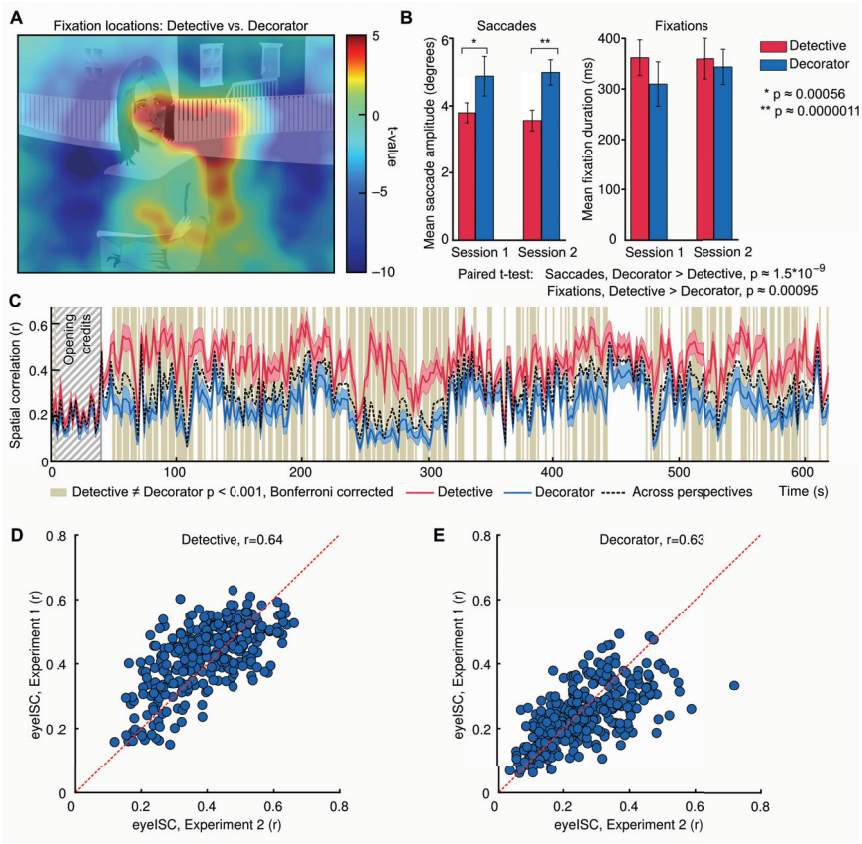

Figure 19. Eye movement patterns across tasks. A: The subtraction heatmaps (T-scores, unthresholded) show regions receiving more fixations in the social (turquoise to blue) and non-social (yellow to red) perspective conditions. Heatmaps were computed over the entire experiment and are here shown overlaid on a sketch of a representative frame of the movie. B: Saccades were longer in the decorator condition and fixations were longer in the detective condition. C: Time courses of inter-subject synchronization (±95% confidence interval) of gaze position within perspectives (red and blue) and across perspectives (black dashed line). Time points with significantly different eyeISC across conditions are indicated by vertical bars. Opening credits are indicated by gray striped background. D and E: Correspondence of eyeISC values in Experiment 1 vs. Experiment 2 in detective and decorator conditions, respectively. Dashed red line indicates the region where eyeISC in both experiments would be of the same magnitude.

When comparing ISC strength between conditions, activity in occipital lobe, STG, STS and the TPJ had higher ISC across participants in the Detective condition. Subjects' brain activities in occipital and inferior temporal regions were

more correlated when they shared the psychological perspective rather than when they viewed the events in the film from different perspectives (Figure 20).

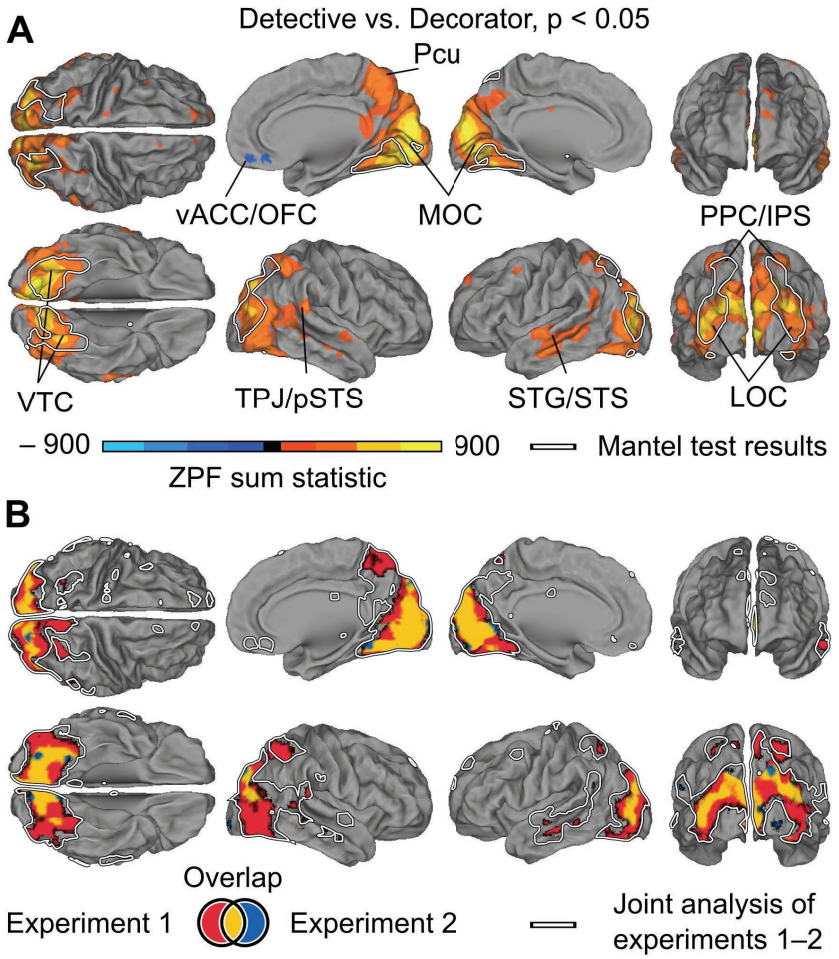

Figure 20. Brain regions exhibiting stronger ISC in the detective vs. decorator perspective (orange to yellow) and vice versa (blue to turquoise). A: Results are calculated on the pooled data of both experiments. Results are thresholded at $p < 0.05$ (FWE controlled). White outlines show areas where ISC was higher within vs. across (see Figure 21). Additional abbreviations: MOC – medial occipital cortex, PPC – posterior parietal cortex, vACC/OFC – ventral anterior cingulate cortex/orbitofrontal cortex, VTC – ventral temporal cortex. B: Areas where ISC was stronger in Detective vs. Decorator perspective in Experiment 1 (red), Experiment 2 (blue) or in both experiments (yellow). White outlines indicate the results based on the pooled data in panel A.

The classification approach confirmed the findings from Mantel test analysis. Higher classification accuracy was found in lateral occipital areas as well as parietal cortex and parahippocampal gyrus (Figure 21 A, Figure 21 C for a scatter plot of the ISC coefficients and classification boundaries). When considering the two experiment separately, classification accuracy was above chance level in both experiments only in lateral occipital cortex (Figure 21 B).

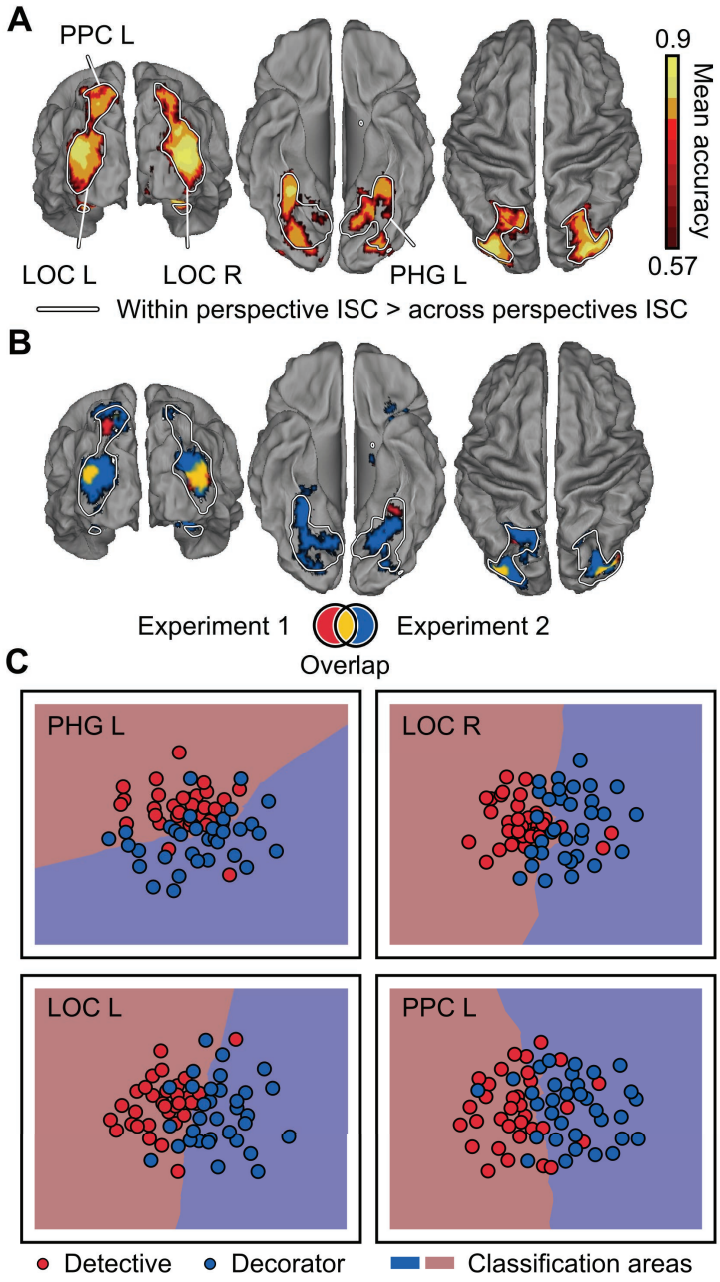

Figure 21. Areas showing higher ISC within vs. across conditions. A: Brain regions where accuracy of voxel-by-voxel classification based on pairwise ISC values calculated over the entire stimulus was significantly above chance level ($p<0.001$, uncorrected) with at least half of the k-values. The color-coding (red— yellow) indicates the average accuracy over the classification results. White outlines indicate areas exhibiting higher within vs. across perspectives ISC in the Mantel test. B: Areas where classification accuracy was significantly above chance level (threshold as in panel A) in Experiment 1 (red), Experiment 2 (blue) or both (yellow). C: Scatter plots show the subjects plotted on a 2D plane using multidimensional scaling where the proximity between two subjects corresponds to their ISC at the brain regions annotated in panel A. Blue and red background colors indicate areas where new subjects would be classified as decorators and detectives, respectively, using a kNN classifier trained on the entire group ($k = 33$).

4.3.4 Conclusions

Taking the same psychological perspective lead to increase in the synchrony of haemodynamic activity in occipital cortex, parahippocampal gyrus, and posterior parietal cortex. Interestingly, the more social Detective perspective resulted in an increase in ISC in the posterior part of the superior temporal sulcus, possibly related to processing of social stimuli. The replication experiment confirmed the reliability of the findings. Results further support the idea that a similar mental state is associated with increased similarity of brain activity.

4.4 Study IV: Reorganization of functionally connected brain subnetworks in high-functioning autism

4.4.1 Aim of the study

The functional neuroimaging literature of ASD reports a mixture of decreased and increased connectivity, often between areas involved in the processing of emotions and social interaction. Here we hypothesized that with the intersubject analysis framework we can take into account the great heterogeneity of individuals with ASD. Furthermore, previous mixed findings are possibly related to a resolution problem with the networks: losing the clear picture by focusing on single nodes or links rather than on the level of larger subnetworks.

4.4.2 Materials and methods

Twenty-six (13 ASD) participants watched a 68-minutes drama feature film ("The Match Factory Girl" by Aki Kaurismäki) containing social cues and interactions. The participants with ASD filled the criteria for Asperger syndrome based on ICD-10 criteria and Autism Quotient (AQ) was obtained for all participants. We then constructed whole brain functional networks by considering 6mm isotropic voxels as nodes covering the whole grey matter (n=5184) and for each pair of nodes a link was computed (n ~=13 millions) as the Pearson's correlation between two node time series. Individual networks were thresholded at 2% density, corresponding to a correlation bigger than ~0.69. We then computed functional subnetworks for each individual with the Louvain algorithm, which maximizes the modularity of the partitions.

We derived group consistent subnetworks using consensus clustering and subnetworks for the control group were matched with existing literature by computing spatial overlap. To test for group differences of subnetworks, we considered the intersubject similarity of each subnetwork defined as the median scaled inclusivity index for the nodes within each control group subnetwork. Furthermore, to take into account intersubject variability in the AQ score, we performed a mantel test with a similarity matrix based on the AQ scores of all participants for each subnetwork. Finally, to test the reproducibility of the findings with a different scanning paradigm and diagnostic tools, we also included extra 27 high functioning (IQ>100) individuals with ASD from the ABIDE resting state dataset. Each individual was diagnosed using ADI-R and ADOS tests. For the sake of completeness, we also computed global network measures (mean link weight, clustering, average path length and efficiency) as well as the value of node strength for each node.

4.4.3 Results

Twelve group-consistent subnetworks were obtained for the control individuals (Figure 22 from bottom to top): 1) Default-mode (DM), 2) Language (LAN), 3) Auditory (AUD), 4) Salience (SAL) 5) Parietal, 6) Dorsal attention (DA), 7) Sensorimotor (SM), 8) Visual primary (V1) 9) Ventro-temporal limbic (VTL) –

comprising subcortical areas (amygdala, nucleus accumbens, putamen, caudate, thalamus) as well as the anterior part of the ventral visual pathway and part of ventro-medial prefrontal cortex 10) Precuneus 11) Cerebellum, and 12) Visual extrastriate (VIS). While there were no significant differences of macro-level graph theoretical properties between subject groups, significant differences were identified in the group intersubject similarity of five subnetworks: DM, AUD, DA, V1, and VTL (see Table 1).

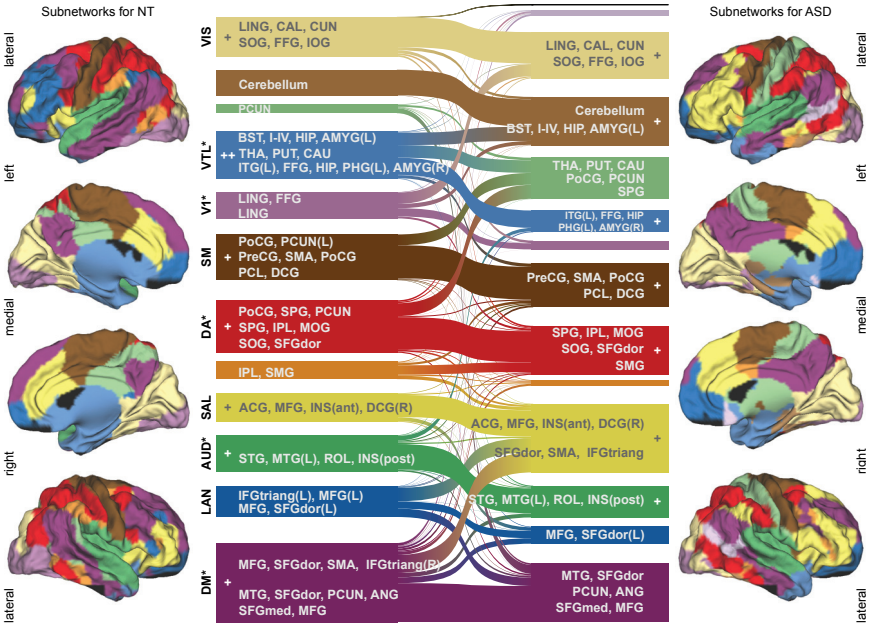

Figure 22. Functional subnetwork similarities and differences between NT (left) and ASD (right) subjects. Subnetworks are color-coded and projected on lateral and medial surfaces. The alluvial diagram in the middle uses the same color-coding. The height of each ribbon representing a subnetwork corresponds to the number of nodes that belong to the given subnetwork. Stars indicate statistically significant group difference: *significant at p<0.05, see also Table 1; plus signs indicate median consistency of all nodes within a subnetwork: +median subnetwork consistency>0.5, ++median subnetwork consistency > 0.75. Ribbons with same color show related areas partitioned into similar subnetworks for both the groups. Acronyms are listed in the beginning of the thesis.

When examining the relationship with the symptoms, subject pairs with more similar AQ subscale scores had more similar VTL subnetwork SI ($r = 0.293$, $p = 0.000297$, see scatter plots in Figure 23). This result was replicated also when including only control subjects ($r = 0.549$, $p = 0.00922$) or only subjects with ASD ($r = 0.257$, $p = 0.0236$), as well as with the reproducibility resting state dataset ($r = 0.17$, $p = 0.0272$).

Subnetwork name	Difference of the means normalized (i.e. t-value)	P-value (via permutations)	Effect size for the difference of the means Hedges'g (95% c.i.)
Default mode (DM)	4.126	2.041e-05*	0.653 (0.377 0.922)
Language (LAN)	0.789	0.218	0.204 (-0.135 0.524)
Auditory (AUD)	4.057	3.759e-05*	0.620 (0.306 0.962)
Salience (SAL)	-0.491	0.3124	0.348 (0.0317 0.671)
Parietal	-0.607	0.2725	-0.024 (-0.33 0.285)
Dorsal attention (DA)	3.014	0.001565*	0.428 (0.117 0.763)
Sensorimotor (SM)	-0.171	0.4327	-0.038 (-0.383 0.3)
Visual primary (V1)	5.788	1.265e-09*	0.537 (0.237 0.874)
Ventro-temporal limbic (VTL)	10.112	8.402e-10*	1.041 (0.709 1.42)
Precuneus	-1.322	0.09558	-0.219 (-0.514 0.0893)
Cerebellum	1.059	0.1457	0.068 (-0.233 0.363)
Visual exstrastriate (VIS)	2.238	0.0137	0.165 (-0.162 0.52)

Table 1. Group difference for NT subnetworks. The table reports group differences for each subnetwork as differences of the mean and effect size with confidence intervals. * = significant with Bonferroni correction at $p < 0.05$.

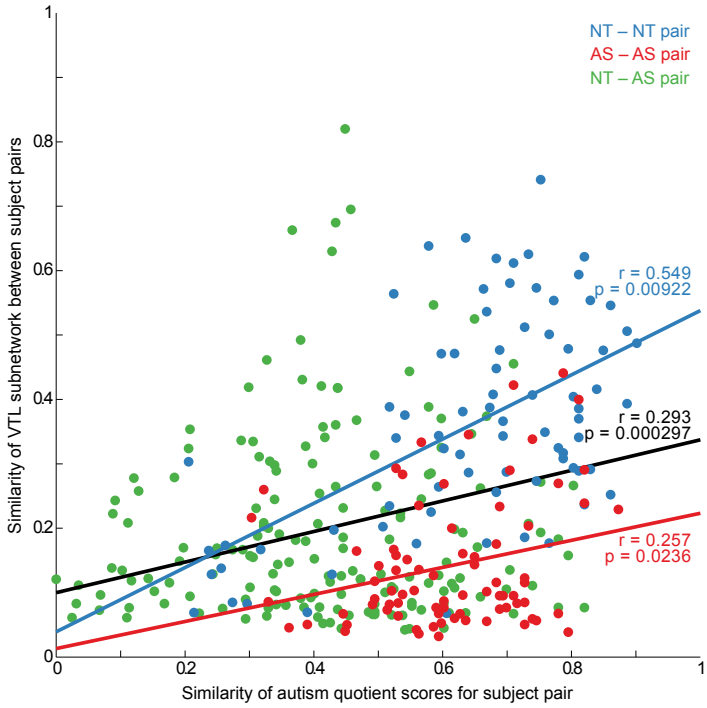

Figure 23. Intersubject analysis between subnetwork similarity and autistic symptoms. Mantel test showing association between VTL subnetwork structure and autistic symptoms. Each dot is a pair of subjects showing their subnetwork similarity with median scaled inclusivity and behavioral similarity with AQ score vectors. Pairs are coded based on within groups (blue NT, red AS) and across groups (green). The Mantel test result in the black interpolation line was performed using all data points. Mantel test results in blue (NT) and red (ASD) interpolation lines are only for within group values. Effect sizes are reported as correlation values and p-values were computed with permutations.

Node and link level results confirmed a general hypo-connectivity in ASD with stronger nodes for controls in anterior cingulate and temporal poles. On the other hand, in subjects with ASD nodes were stronger in posterior cingulate, superior dorsal and inferior dorsal areas (Figure 24 A). Links were in general stronger for controls, although there were also stronger connections for example within MFG and SFGdor or for links between FFG and middle temporal areas (Figure 24 B).

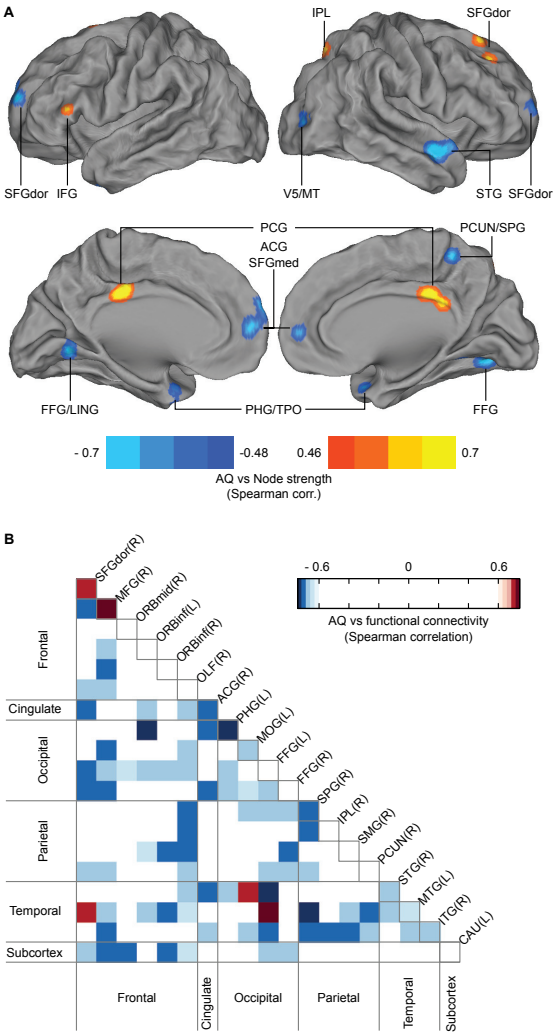

Figure 24. Node-level and link-level regression with autism quotient scores. (A) Map of nodes whose strength values correlate with individual AQ scores. (B) Summary plot of link weight correlations with individual AQ scores. Only the strongest positively and negatively correlated links are reported (links in the 1st percentile). Each element of the pairwise connectivity matrix indicates the average of the correlations between AQ and link weights for all the links between a pair of anatomical regions. The main diagonal shows the average correlation for links within the respective region.

4.4.4 Conclusions

By modeling haemodynamic activity as a functional network without any apriori assumption on the nodes or the links, we showed significant reorganization of VTL and DM subnetworks in patients with autism spectrum disorder. The reconfiguration of the VTL subnetwork correlated with the severity of autistic symptoms also within the control group, possibly related to lower prosocial behavior as well as personality traits. Micro-level results confirmed the mixture of hypo- and hyper- connectivity. The subnetwork-level analysis provided information that was not visible at microscopic level, proposing a possible solution for other spectrum disorders related to neuronal connectivity dysfunction and with high heterogeneity of symptoms (e.g. schizophrenia).

5. Discussion

In these studies I suggest a set of novel methods for quantifying dynamic similarity between brain activity across individuals. These methods allow us also to discover what is shared and what is idiosyncratic in the brain activity of healthy and clinical populations. By using for the first time time-varying intersubject correlation, Study I showed how extrinsic stimulation with strong emotional content dynamically synchronized brain activity across subjects by modulating regions involved in emotion processing as well as large scale subnetworks such as the default mode and dorsal attention. Study II proposed a new method to improve temporal resolution of intersubject similarity for local level activity and for dynamic functional connectivity. By using the full similarity matrix between BOLD responses of pairs of subjects, Study III tested how active perspective-taking synchronizes the brain activity of people sharing the same mental perspective. Finally, Study IV extended the intersubject analysis framework and moved from voxels to network activity, by quantifying the similarity between brain subnetworks in relation to the similarity of the autism quotient score. This approach is a possible solution for the quantification of intra-individual differences to account for the individual variance, which is necessary in high heterogeneous spectrum disorders like Autism. Furthermore, all studies used dynamic naturalistic stimuli for greater ecological validity of the findings as well as to elicit lifelike complex cognitive processes.

5.1 Emotions synchronize our brains

Study I identified dynamic intersubject correlation elicited by emotions as a possible mechanisms at the basis of empathy and understanding of the intentions of others. Strong emotions elicited synchronous brain activity that was modulated by the emotional dimensions of valence and arousal in a spatio-temporally independent fashion. Arousing events, by increasing the synchrony in attention circuits and somatosensory cortices, capture covert and overt attention (Nummenmaa et al., 2006; Brosch et al., 2007) and also reveal the role of the body in the encoding of emotional states (Nummenmaa et al., 2008; Johnsen et al., 2009; Nummenmaa et al., 2014a).

On the other hand, negative valence increased synchrony in the default mode subnetwork (DM). The role of DM is clearly beyond that of a network being

present during lack of task. DM has been found in multiple species such as non-human primates, cats and rodents (Raichle, 2015). It has been argued however that DM is at the heart of what makes “the human animal human” since it is involved in self referential mental activity, self awareness, consciousness, mind wandering, creativity (Callard and Margulies, 2014). Areas belonging to the DM subnetwork are also activated during social cognition and theory of mind tasks (Mars et al., 2012). When considering the dynamics of the DM subnetwork in relationship to other subnetworks, recent evidence points towards the salience subnetwork modulating the relationship between DM and executive subnetwork as well as the important role of basal ganglia and thalamus in the switching between "default" and more "attentive" states (Di and Biswal, 2014). This is in line with our results with arousal-modulated ISC in dorsal attention areas and valence-modulated ISC in the self-referential and social processing DM subnetwork. Negative emotions were also correlated with an increased ISC in frontal areas, possibly related to a more automatic fight-or-flight response as well as to a more individual way of relating to the content of the stimuli (Schippers et al., 2010) as identified in the ISA framework analysis by considering the subtle inter-subject differences in the perceived valence of the stimuli (Figure 13).

Although studies have shown that highly engaging complex stimuli are able to synchronize areas beyond sensory cortices (Hasson et al., 2004, 2010), only by adding the temporal dimension we were able to disentangle the synchronous brain areas involved across the whole experiment (Figure 10) and identify those specifically related to valence and arousal (Figure 11). The approach of this study have set the bases for a subsequent study: in (Nummenmaa et al., 2014b) emotional audio stories were eliciting intersubject phase-synchronization. The results were compatible with what was found with movie clips in Study I: positively correlated synchronization with arousal was also present in primary sensory (auditory in this case, while in Study I visual) and executive-control areas, while negative valence was again associated with midline structures from DM subnetwork as well as medial parieto-occipital areas.

5.2 The temporal dimension in inter-individual similarities

Both Study I and Study II explored the temporal dimension in intersubject similarity of brain activation time series, although with two different methods. ISC, intuitive and elegant in its simplicity, has become an important tool in fMRI analysis. The data driven approach of correlating each subject activity time series with the others, identifies in a purely data-driven fashion what is significantly activated and is comparable to a general linear model approach (Pajula et al., 2012). ISC however is going to tell us which areas reliably activated across the whole experiment, without separating the actual dynamics of each area: in some time points some areas might be ISC correlated while others are not correlated, and vice versa, as we saw in the results of Study I.

The phase synchronization approach extended the sliding window method by considering the instantaneous phase property of the analytic signal. Despite the necessary compromise of narrow band filtering, IPS revealed to be useful in successive studies with fast designs. In (Nummenmaa et al., 2014c), for example, we compared the performance of IPS and sliding window ISC and IPS was able to identify brain areas involved in the study task (mentally simulating the activity of one of the two opponents during a boxing match, while the video of the match was shown). ISC temporal windows had to be longer than the trial duration so frontal and anterior-temporal-lobe effects were completely missed.

Furthermore, the dynamic connectivity measure proposed – SBPS – enabled the investigation of time-varying connectivity without the constraints of a sliding window or assumptions based on external models (as in, for example generalized psychophysiological interaction, McLaren et al., 2012). The SBPS method was successively applied to naturalistic dataset (Nummenmaa et al., 2014b, 2014c), as well as adopted by other labs to develop computational models for resting state to study the ultra slow (<0.01Hz) dynamics of global phase synchronization of BOLD signal (Ponce-Alvarez et al., 2015). Another recent method paper extended our findings using a time-frequency phase synchrony approach with resting state data (Villafane-Delgado et al., 2014). The main advantage of these methods is that IPS and SBPS are single trial data driven approaches, which are necessary when stimuli are very complex and there is no repetition of any event whatsoever.

5.3 Intrinsic mentalization and shared mental representations

The concept of mental representations and representational theory of mind has existed in philosophy since Aristotle (Pitt, 2013). More recently, neuroscientific studies have studied representations in the brain with fMRI both related for shared semantic categories (Stephens et al., 2010; Stansbury et al., 2013) as well as individual representations of visual information (Charest et al., 2014). Our results from Study III and Study I and subsequent studies using the methods from Study II are in line with this conceptual framework, but extend it to the temporal dimension: it is not just a pattern of activation that is consistently evoked in an individual subject, it is the temporal dynamics of BOLD activity that is time locked across subjects sharing the same perspective. The advantage of using a representational similarity framework is that representations are a second order isomorphism (Kriegeskorte et al., 2008): what is compared is not a brain signal with some model signal belonging from two different worlds, it is their representation that is matched. This approach is at the core of the Mantel test in ecology: two measurements (geographical location of different species of insects and their genome) are not compared directly; it is the similarity between pairs of insects that is considered and whether the geographical similarity correlated with genetic similarity. The approach has been successfully applied in genetics for genome wide association studies where the similarity of phenotypic traits is compared to the similarity of genes

expressions (Zapala and Schork, 2006). This framework is elegant in its simplicity: not only we skip the difficult step of trying to match signals from different domains (brain activity and ideal models), furthermore it is easier to interpret the results from these comparisons (Zapala and Schork, 2012) rather than trying to understand the "importance weights" of a neuronal network or other machine learning approaches (Norman et al., 2006).

5.4 Similarity of subnetworks in healthy and clinical populations

Study IV extends the suggestion on the advantages of using distance metrics from the previous section to networks: rather than finding a straight relationship between an individual phenotype and a network property, we developed the intersubject analysis framework (Figure 7) to test for the similarity between individuals. Coincidentally, a similar framework - named connectome wise association studies (Shehzad et al., 2014) – has also been recently proposed. The problem with individuals with ASD is in the great variability of the diseases at genetic and imaging levels (Hernandez et al., 2014), which introduces the problem of what to consider similar between highly idiosyncratic autistic individuals.

Large scale efforts have been adopted using structural imaging (Haar et al., 2014) and no results have been found for the average brain of an individual with ASD performing group comparisons with standard statistical tools. Possibly, considering the variance within the ASD group could reveal areas with structural differences at voxel level. Functional studies on the other hand have recently been considering the individual idiosyncrasies in ASDs (Salmi et al., 2013; Hahamy et al., 2015; Byrge et al., 2015) and our Study IV is continuing on the lines traced by these early efforts. By looking at the level of subnetworks we tried to move from the individual variability that is present at the microscopic level (nodes and links) in ASD individuals towards mesoscopic-level differences that are consistent across subjects. Interestingly, the VTL subnetwork – comprising subcortical areas (amygdala, nucleus accumbens, putamen, caudate, thalamus) as well as the anterior part of the ventral visual pathway and part of ventro-medial prefrontal cortex – was the only one covarying with the similarity of participant's AQ and ADI-R ADOS scores. VTL regions have been known to be important in ASD for a long time (Courchesne, 1997) as they are part of distributed networks involved in social cognition (Gotts et al., 2012; Kennedy and Adolphs, 2012). The 'social motivation' circuit – amygdala, striatum and orbito-frontal cortex – has also been suggested to be affected in ASD (Chevallier et al., 2012), pointing to the important role of the striatum in ASD individuals in recent imaging (Zhou et al., 2014) and genetic (Willsey and State, 2015) studies. Furthermore, the same pattern of inter-subject similarity predicted by the AQ score was also present in NT participants, possibly related to lower prosocial behavior (Jameel et al., 2014) as well as personality traits (Kennis et al., 2013). Taking into account all intersubject variance of subnetworks might provide interesting findings with other spectrum of disorders, like

schizophrenia, that are characterized by high heterogeneity of symptoms and are possibly caused by neuronal connectivity dysfunction (Marín, 2012).

5.5 Challenges and limitations

Few methodological observations might be raised. First of all, the use of naturalistic stimuli goes hand in hand with the lack of controllability of all the possible features and other factors involved. Furthermore, different features might be correlated with each other; hence it becomes impossible to disentangle all the effects in a similar fashion as in controlled studies (Lahnakoski et al., 2012b). A combination of controlled task localizing regions of interest in the experiments and naturalistic stimuli might be the way to go by firstly testing which areas are involved in a specific task and then see how they behave under a more natural condition or in patients who are not able to perform the task, but are able to passively follow the complex stimuli (Naci et al., 2014). Furthermore, it is also important to measure subjects' behavior as we did in Study I with our novel web-based annotation tool. It is still a concern however that this cannot be done concomitantly during scanning, since other neuronal processing (e.g. moving a slider while watching the movie) will necessarily induce activations that are not related to a lifelike condition. One has also to notice that the paradigm-free approach of ISC cannot imply any causal effect between "brain ticking together" and mutual understanding (Stolk, 2014). While our methods are able to show that the synchronization that happens between subjects is quantitative and not just a qualitative metaphor, we are still few steps away from the logic "similar neuronal representations cause mutual understanding". In general the concept of mental representations has vast implications touching also psychology and philosophy so that is impossible to tell what comes first: the mental representation or the concept that we are trying to represent and communicate. Also in this case, clever and novel experimental paradigms should be devised to assess the continuum space of the level of mutual understanding between a pair of subjects in a "two-person" neuroscience approach (Hari and Kujala, 2009; Hasson et al., 2012; Schilbach et al., 2013).

When moving from temporal average statistics to analysis of instantaneous events with the methods proposed in study II, one must also seriously take into account possible confounds such as head motion or physiological changes that instantly co-varying with the stimulus. This will be even more important when more interactive lifelike paradigms like story-telling inside the scanner (Stephens et al., 2010) are adopted. Head motion artifacts are even a bigger concern when it comes to connectivity (Power et al., 2014) by affecting the level of correlation between time series, usually increasing the value of short distance links and decreasing long distance connections (Power et al., 2012). Even when controlling for head motion by regressing out motion parameters and removing time points affected by motion (known as *scrubbing*) the whole picture is not simple as other preprocessing steps, like smoothing (Scheinost et

al., 2014) might affect the final connectivity values. Recent discussions point towards using ICA based de-noising, by automatically identify noisy independent components and then removing them (Pruim et al., 2015). This is important since simple regression of head motion parameters might affect all voxels especially for short dataset by removing actual neuronal signal. With only a few time points, there is higher chance that a voxel time series can be correlated with any confound time series, de facto producing "noise" with the same network structure as the real neuronal signals (Bright and Murphy, 2015).

The introduction of the temporal dimension in IPS for intersubject synchronization as well as SBPS for dynamic functional connectivity came with the necessary trade-off of the band pass filtering of the signal. Although we provided literature-based evidence of the fact that the most stable frequency range of BOLD spectrum is in the slow-4 (0.027 – 0.073 Hz) range, further studies should be carried on what are the roles of these sub-bands, although first attempts are already seen (Xue et al., 2014). Regions that integrate information over longer time-scales (in the order of tens of seconds – $f < 0.04$ Hz) such as precuneus and temporo-parietal junction (Stephens et al., 2013) might be affected by band pass filtering. Novel methods that perform a full spectrotemporal decomposition of time series could be better suited to explore frequency specific instantaneous synchronization. Moreover, as BOLD depends on cerebral blood flow and oxygen consumption rate, only by combining multiple measures the role of oscillatory processes in the BOLD signal can be clarified. Recent evidence seems to point towards the fact that local oxygen fluctuations are happening with a 0.06 Hz narrowband component, which is responsible in driving inter-regional correlations (Li et al., 2015).

Finally, spectrum diseases such as ASD are calling for accounting possible sub-types and sub-groups of individuals within the umbrella name of autism (Lai et al., 2013). It is still not known if such grouping should become from genetic or imaging data or from behavior. Mostly a combination of all the three approaches will help to clarify the differences across individuals with the same diagnosis and outline possible specialized interventions. Only recent research is adopting large scale machine learning methods to understand the sub-dimensions of current autism diagnostic tools (Kosmicki et al., 2015) while there are not yet equivalent studies using brain imaging or genetics.

6. General conclusions

As many other features of living organisms, the brain has evolved with remarkable similarity of structure and function across and between species. By adding the temporal dimension in the quantification of similarity of brain activity, we identify not only which areas consistently activate across people, but also when are the salient moments that make us tick in sync. By then extending the intersubject correlation method with instantaneous phase synchronization, we reveal with more precision the moments of shared experience, despite the inherent limitations of the BOLD signal. Similarity though comes hand in hand with difference; with the intersubject analysis framework we are able to identify similarities and differences in brain activations that correlate with similarity and differences in behavior, by considering pairs of subjects. When moving from local brain activity to the level of interaction between multiple brain regions, we extended the intersubject similarity framework to measure the similarity of functional subnetworks. We demonstrated this by studying the subnetwork similarity between pairs of individuals with autism and identified the ventro-temporal limbic subnetwork whose layout was correlated with the autism quotient score, both within patients and controls. The combination of all these methods sets a solid ground for future studies where intersubject similarity of time-varying brain networks will bring us closer to the actual functioning of the brain, revealing the common neuronal code as a function of behavioral differences between subjects and as a function of the temporal dynamics of the events occurring around us.

References

Achard, S., Delon-Martin, C., Vértes, P.E., Renard, F., Schenck, M., Schneider, F., Heinrich, C., Kremer, S., Bullmore, E.T., 2012. Hubs of brain functional networks are radically reorganized in comatose patients. Proc. Natl. Acad. Sci. U. S. A. 109, 20608–13. doi:10.1073/pnas.1208933109

Achard, S., Salvador, R., Whitcher, B., Suckling, J., Bullmore, E., 2006. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J. Neurosci. Off. J. Soc. Neurosci. 26, 63–72. doi:10.1523/JNEUROSCI.3874-05.2006

Aguirre, G.K., Zarahn, E., D'esposito, M., 1998. The variability of human, BOLD hemodynamic responses. NeuroImage 8, 360–9. doi:10.1006/nimg.1998.0369

Ahn, Y.-Y., Bagrow, J.P., Lehmann, S., 2010. Link communities reveal multiscale complexity in networks. Nature 466, 761–4. doi:10.1038/nature09182

Alexander-Bloch, A., Lambiotte, R., Roberts, B., Giedd, J., Gogtay, N., Bullmore, E., 2012. The discovery of population differences in network community structure: New methods and applications to brain functional networks in schizophrenia. NeuroImage 59, 3889–3900. doi:10.1016/j.neuroimage.2011.11.035

Alluri, V., Toiviainen, P., Jääskeläinen, I.P., Glerean, E., Sams, M., Brattico, E., 2012. Large-scale brain networks emerge from dynamic processing of musical timbre, key and rhythm. NeuroImage 59, 3677–89. doi:10.1016/j.neuroimage.2011.11.019

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E., 2001. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Malesand Females, Scientists and Mathematicians. J. Autism Dev. Disord. 31, 5–17.

Bartels, A., Zeki, S., 2004. Functional brain mapping during free viewing of natural scenes. Hum. Brain Mapp. 21, 75–85. doi:10.1002/hbm.10153

Beckmann, C.F., DeLuca, M., Devlin, J.T., Smith, S.M., 2005. Investigations into resting-state connectivity using independent component analysis. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360, 1001–13. doi:10.1098/rstb.2005.1634

Bedrosian, E., 1962. A product theorem for Hilbert transforms. Proc. IEEE 74, 520–521. doi:10.1109/PROC.1986.13495

Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J. R. Stat. Soc. Ser. B 57, 289–300.

Birn, R.M., Diamond, J.B., Smith, M.A., Bandettini, P.A., 2006. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31, 1536–1548.

Biswal, B.B., 2012. Resting state fMRI: a personal history. NeuroImage 62, 938–44. doi:10.1016/j.neuroimage.2012.01.090

Biswal, B., DeYoe, a E., Hyde, J.S., 1996. Reduction of physiological fluctuations in fMRI using digital filters. Magn. Reson. Med. Off. J. Soc. Magn. Reson. Med. Soc. Magn. Reson. Med. 35, 107–13.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. Off. J. Soc. Magn. Reson. Med. Soc. Magn. Reson. Med. 34, 537–41.

Blockley, N.P., Griffeth, V.E.M., Simon, A.B., Buxton, R.B., 2013. A review of calibrated blood oxygenation level-dependent (BOLD) methods for the measurement of task-induced changes in brain oxygen metabolism. NMR Biomed. 26, 987–1003. doi:10.1002/nbm.2847

Bright, M.G., Murphy, K., 2015. Is fMRI "noise" really noise? Resting state nuisance regressors remove variance with network structure. NeuroImage. doi:10.1016/j.neuroimage.2015.03.070

Brosch, T., Sander, D., Scherer, K.R., 2007. That baby caught my eye... attention capture by infant faces. Emot. Wash. DC 7, 685–9. doi:10.1037/1528-3542.7.3.685

Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R. a, Johnson, K. a, 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J. Neurosci. Off. J. Soc. Neurosci. 29, 1860–73. doi:10.1523/JNEUROSCI.5062-08.2009

Bullmore, E., Sporns, O., 2012. The economy of brain network organization. Nat. Rev. Neurosci. 13, 336–49. doi:10.1038/nrn3214

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–98. doi:10.1038/nrn2575

Buxton, R.B., Wong, E.C., Frank, L.R., 1998. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magn. Reson. Med. Off. J. Soc. Magn. Reson. Med. Soc. Magn. Reson. Med. 39, 855–64.

Byrge, L., Dubois, J., Tyszka, J.M., Adolphs, R., Kennedy, D.P., 2015. Idiosyncratic Brain Activation Patterns Are Associated with Poor Social Comprehension in Autism. J. Neurosci. 35, 5837–5850. doi:10.1523/JNEUROSCI.5182-14.2015

Cabral, J., Hugues, E., Sporns, O., Deco, G., 2011. Role of local network oscillations in resting-state functional connectivity. NeuroImage 57, 130–9. doi:10.1016/j.neuroimage.2011.04.010

Callard, F., Margulies, D.S., 2014. What we talk about when we talk about the default mode network. Front. Hum. Neurosci. 8, 619. doi:10.3389/fnhum.2014.00619

Charest, I., Kievit, R.A., Schmitz, T.W., Deca, D., Kriegeskorte, N., 2014. Unique semantic space in the brain of each beholder predicts perceived similarity. Proc. Natl. Acad. Sci. U. S. A. 111, 14565–70. doi:10.1073/pnas.1402594111

Chen, J.E., Chang, C., Greicius, M.D., Glover, G.H., 2015. Introducing co-activation pattern metrics to quantify spontaneous brain network dynamics. NeuroImage 111, 476–488. doi:10.1016/j.neuroimage.2015.01.057

Chen, S., Ma, B., Zhang, K., 2009. On the similarity metric and the distance metric. Theor. Comput. Sci. 410, 2365–2376. doi:10.1016/j.tcs.2009.02.023

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E.S., Schultz, R.T., 2012. The social motivation theory of autism. Trends Cogn. Sci. 16, 231 – 239. doi:http://dx.doi.org/10.1016/j.tics.2012.02.007

Courchesne, E., 1997. Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. Curr. Opin. Neurobiol. 7, 269 – 278. doi:http://dx.doi.org/10.1016/S0959-4388(97)80016-5

Craddock, R.C., Jbabdi, S., Yan, C.-G., Vogelstein, J.T., Castellanos, F.X., Di Martino, A., Kelly, C., Heberlein, K., Colcombe, S., Milham, M.P., 2013. Imaging human connectomes at the macroscale. Nat. Methods 10, 524–539. doi:10.1038/nmeth.2482

Di, X., Biswal, B.B., 2014. Modulatory interactions between the default mode network and task positive networks in resting-state. PeerJ 2, e367.

Dolan, K., Spano, M., 2001. Surrogate for nonlinear time series analysis. Phys. Rev. E 64, 1–6. doi:10.1103/PhysRevE.64.046128

Falan, S., 2010. Concept Analysis of Similarity Applied to Nursing Diagnoses: Implications for Educators. Int. J. Nurs. Terminol. Classif. 21, 144–155. doi:10.1111/j.1744-618X.2010.01163.x

Fortunato, S., Castellano, C., 2007. Community Structure in Graphs. Networks 42.

Friston, K.J., Mechelli, A., Turner, R., Price, C.J., 2000. Nonlinear responses in fMRI: the Balloon model, Volterra kernels, and other hemodynamics. NeuroImage 12, 466–77. doi:10.1006/nimg.2000.0630

Furman, O., Dorfman, N., Hasson, U., Davachi, L., Dudai, Y., 2007. They saw a movie: Long-term memory for an extended audiovisual narrative. Learn. Mem. 14, 457–467. doi:10.1101/lm.550407

Gillham, N.W., 2001. A Life of Sir Francis Galton: From African Exploration to the Birth of Eugenics. Oxford University Press, New York.

Good, P., Wang, R.J., 2005. Permutation, parametric and bootstrap tests of hypotheses, Springer Series in Statistics. Springer New York:, New York.

Gotts, S.J., Saad, Z.S., Jo, H.J., Wallace, G.L., Cox, R.W., Martin, A., 2013. The perils of global signal regression for group comparisons: a case study of Autism Spectrum Disorders. Front. Hum. Neurosci. 7, 356. doi:10.3389/fnhum.2013.00356

Gotts, S.J., Simmons, W.K., Milbury, L.A., Wallace, G.L., Cox, R.W., Martin, A., 2012. Fractionation of social brain circuits in autism spectrum disorders. Brain J. Neurol. 135, 2711–25. doi:10.1093/brain/aws160

Graham, D.W., 2011. Heraclitus, in: Zalta, E.N. (Ed.), The Stanford Encyclopedia of Philosophy.

Haar, S., Berman, S., Behrmann, M., Dinstein, I., 2014. Anatomical Abnormalities in Autism? Cereb. Cortex N. Y. N 1991. doi:10.1093/cercor/bhu242

Hahamy, A., Behrmann, M., Malach, R., 2015. The idiosyncratic brain: distortion of spontaneous connectivity patterns in autism spectrum disorder. Nat. Neurosci. 18, 302–309. doi:10.1038/nn.3919

Han, C.E., Yoo, S.W., Seo, S.W., Na, D.L., Seong, J.-K., 2013. Cluster-based statistics for brain connectivity in correlation with behavioral measures. PloS One 8, e72332. doi:10.1371/journal.pone.0072332

Hanson, L.G., 2008. Is quantum mechanics necessary for understanding magnetic resonance? Concepts Magn. Reson. Part A 32A, 329–340. doi:10.1002/cmr.a.20123

Hari, R., Kujala, M.V., 2009. Brain basis of human social interaction: from concepts to brain imaging. Physiol. Rev. 89, 453–79. doi:10.1152/physrev.00041.2007

Hari, R., Parkkonen, L., 2015. The brain timewise: how timing shapes and supports brain function. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 370, 20140170–. doi:10.1098/rstb.2014.0170

Hasson, U., Avidan, G., Gelbard, H., Vallines, I., Harel, M., Minshew, N., Behrmann, M., 2009. Shared and idiosyncratic cortical activation patterns in autism revealed under continuous real-life viewing conditions. Autism Res. Off. J. Int. Soc. Autism Res. 2, 220–31. doi:10.1002/aur.89

Hasson, U., Ghazanfar, A.A., Galantucci, B., Garrod, S., Keysers, C., 2012. Brain-to-brain coupling: a mechanism for creating and sharing a social world. Trends Cogn. Sci. 16, 114–21. doi:10.1016/j.tics.2011.12.007

Hasson, U., Landesman, O., Knappmeyer, B., Vallines, I., Rubin, N., Heeger, D.J., 2008a. Neurocinematics: The neuroscience of film. Projections 2, 1–26.

Hasson, U., Malach, R., Heeger, D.J., 2010. Reliability of cortical activity during natural stimulation. Trends Cogn. Sci. 14, 40–8. doi:10.1016/j.tics.2009.10.011

Hasson, U., Nir, Y., Levy, I., Fuhrmann, G., Malach, R., 2004. Intersubject Synchronization of Cortical Activity During Natural Vision. Science 303, 1634–1640.

Hasson, U., Yang, E., Vallines, I., Heeger, D.J., Rubin, N., 2008b. A hierarchy of temporal receptive windows in human cortex. J. Neurosci. Off. J. Soc. Neurosci. 28, 2539–50. doi:10.1523/JNEUROSCI.5487-07.2008

Henrich, J., Heine, S.J., Norenzayan, A., 2010. The weirdest people in the world? Behav. Brain Sci. 33, 61–83; discussion 83–135. doi:10.1017/S0140525X0999152X

Hernandez, L.M., Rudie, J.D., Green, S. a, Bookheimer, S., Dapretto, M., 2014. Neural Signatures of Autism Spectrum Disorders: Insights into Brain Network Dynamics. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 40, 1–82. doi:10.1038/npp.2014.172

Hill, R.A., Dunbar, R.I.M., 2003. Social network size in humans. Hum. Nat. 14, 53–72. doi:10.1007/s12110-003-1016-y

Hoge, R.D., 2012. Calibrated FMRI. NeuroImage 62, 930–7. doi:10.1016/j.neuroimage.2012.02.022

Huettel, S., Song, A., Mccarthy, G., 2004. Functional Magnetic Resonance Imaging. {Sinauer Associates}.

Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Della Penna, S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., Handwerker, D.A., Keilholz, S., Kiviniemi, V., Leopold, D.A., de Pasquale, F., Sporns, O., Walter, M., Chang, C., 2013. Dynamic functional connectivity: Promise, issues, and interpretations. NeuroImage 80, 360–378. doi:10.1016/j.neuroimage.2013.05.079

Jameel, L., Vyas, K., Bellesi, G., Roberts, V., Channon, S., 2014. Going “Above and Beyond”: Are Those High in Autistic Traits Less Pro-social? J. Autism Dev. Disord. 44, 1846–1858.

Johnsen, E.L., Tranel, D., Lutgendorf, S., Adolphs, R., 2009. A neuroanatomical dissociation for emotion induced by music. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 72, 24–33. doi:10.1016/j.ijpsycho.2008.03.011

Kanai, R., Rees, G., 2011. The structural basis of inter-individual differences in human behaviour and cognition. Nat. Rev. Neurosci. 12, 231–42. doi:10.1038/nrn3000

Kauppi, J., Jääskeläinen, I.P., Sams, M., Tohka, J., 2010. Inter-subject correlation of brain hemodynamic responses during watching a movie: localization in space and frequency. Front. Neuroinformatics 4, 5. doi:10.3389/fninf.2010.00005

Kauppi, J.-P., Pajula, J., Tohka, J., 2014. A versatile software package for inter-subject correlation based analyses of fMRI. Front. Neuroinformatics 8, 2. doi:10.3389/fninf.2014.00002

Kennedy, D.P., Adolphs, R., 2012. The social brain in psychiatric and neurological disorders. Trends Cogn. Sci. 16, 559 – 572. doi:http://dx.doi.org/10.1016/j.tics.2012.09.006

Kennis, M., Rademaker, A.R., Geuze, E., 2013. Neural correlates of personality: an integrative review. Neurosci. Biobehav. Rev. 37, 73–95. doi:10.1016/j.neubiorev.2012.10.012

Kitzbichler, M.G., Smith, M.L., Christensen, S. ren R., Bullmore, E., 2009. Broadband criticality of human brain network synchronization. PLoS Comput. Biol. 5, e1000314. doi:10.1371/journal.pcbi.1000314

Kosmicki, J.A., Sochat, V., Duda, M., Wall, D.P., 2015. Searching for a minimal set of behaviors for autism detection through feature selection-based machine learning. Transl. Psychiatry 5, e514. doi:10.1038/tp.2015.7

Krieger, S.N., Gauthier, C.J., Ivanov, D., Huber, L., Roggenhofer, E., Sehm, B., Turner, R., Egan, G.F., 2014. Regional reproducibility of calibrated BOLD functional MRI: implications for the study of cognition and plasticity. NeuroImage 101, 8–20. doi:10.1016/j.neuroimage.2014.06.072

Kriegeskorte, N., Mur, M., Bandettini, P., 2008. Representational similarity analysis - connecting the branches of systems neuroscience. Front. Syst. Neurosci. 2, 4. doi:10.3389/neuro.06.004.2008

Lahnakoski, J.M., Glerean, E., Salmi, J., Jääskeläinen, I.P., Sams, M., Hari, R., Nummenmaa, L., 2012a. Naturalistic FMRI mapping reveals superior temporal sulcus as the hub for the distributed brain network for social perception. Front. Hum. Neurosci. 6.

Lahnakoski, J.M., Salmi, J., Jääskeläinen, I.P., Lampinen, J., Glerean, E., Tikka, P., Sams, M., 2012b. Stimulus-Related Independent Component and Voxel-Wise Analysis of Human Brain Activity during Free Viewing of a Feature Film. PLoS ONE 7, e35215. doi:10.1371/journal.pone.0035215

Lai, M.-C., Lombardo, M.V., Chakrabarti, B., Baron-Cohen, S., 2013. Subgrouping the Autism "Spectrum": Reflections on DSM-5. PLoS Biol 11, e1001544. doi:10.1371/journal.pbio.1001544

Leonardi, N., Van De Ville, D., 2015. On spurious and real fluctuations of dynamic functional connectivity during rest. NeuroImage 104, 430–6. doi:10.1016/j.neuroimage.2014.09.007

Li, J.M., Bentley, W.J., Snyder, A.Z., Raichle, M.E., Snyder, L.H., 2015. Functional connectivity arises from a slow rhythmic mechanism. Proc. Natl. Acad. Sci. U. S. A. doi:10.1073/pnas.1419837112

Logothetis, N.K., 2008. What we can do and what we cannot do with fMRI. Nature 453, 869–78. doi:10.1038/nature06976

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., Schopler, E., 1989. Austism diagnostic observation schedule: A standardized observation of communicative and social behavior. J. Autism Dev. Disord. 19, 185–212.

Lord, C., Rutter, M., Le Couteur, A., 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J. Autism Dev. Disord. 24, 659–685.

Mantel, N., 1967. The detection of disease clustering and a generalized regression approach. Cancer Res. 27, 209–220. doi:10.1038/214637b0

Marín, O., 2012. Interneuron dysfunction in psychiatric disorders. Nat Rev Neurosci 13, 107–120. doi:10.1038/nrn3155

Mars, R.B., Neubert, F.-X., Noonan, M.P., Sallet, J., Toni, I., Rushworth, M.F.S., 2012. On the relationship between the "default mode network" and the "social brain". Front. Hum. Neurosci. 6, 189. doi:10.3389/fnhum.2012.00189

Mates, B., 1989. The Philosophy of Leibniz: Metaphysics and Language. Oxford Univ. Press, Oxford.

Maximo, J.O., Cadena, E.J., Kana, R.K., 2014. The implications of brain connectivity in the neuropsychology of autism. Neuropsychol. Rev. 24, 16–31. doi:10.1007/s11065-014-9250-0

McLaren, D.G., Ries, M.L., Xu, G., Johnson, S.C., 2012. A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. NeuroImage 61, 1277–86. doi:10.1016/j.neuroimage.2012.03.068

Mehrabian, A., Epstein, N., 1972. A measure of emotional empathy1. J. Pers. 40, 525–543. doi:10.1111/j.1467-6494.1972.tb00078.x

Mesulam, M.M., 1990. Large-Scale Neurocognitive Networks and Distributed Processing for Attention, Language, and Memory. Ann. Neurol. 28, 597–613.

Mitchell, K.J., 2007. The genetics of brain wiring: from molecule to mind. PLoS Biol. 5, e113. doi:10.1371/journal.pbio.0050113

Moussa, M.N., Steen, M.R., Laurienti, P.J., Hayasaka, S., 2012. Consistency of Network Modules in Resting-State fMRI Connectome Data. PLoS ONE 7, e44428. doi:10.1371/journal.pone.0044428

Naci, L., Cusack, R., Anello, M., Owen, A.M., 2014. A common neural code for similar conscious experiences in different individuals. Proc. Natl. Acad. Sci. U. S. A. 111, 14277–82. doi:10.1073/pnas.1407007111

Newman, M.E.J., 2003. The structure and function of complex networks. SIAM Rev. 45, 167–256.

Nichols, T., Hayasaka, S., 2003. Controlling the familywise error rate in functional neuroimaging: a comparative review. Stat. Methods Med. Res. 12, 419–446. doi:10.1191/0962280203sm341ra

Norman, K.A., Polyn, S.M., Detre, G.J., Haxby, J.V., 2006. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cogn. Sci. 10, 424–30. doi:10.1016/j.tics.2006.07.005

Nummenmaa, L., Glerean, E., Hari, R., Hietanen, J.K., 2014a. Bodily maps of emotions. Proc. Natl. Acad. Sci. U. S. A. 111, 646–51. doi:10.1073/pnas.1321664111

Nummenmaa, L., Glerean, E., Viinikainen, M., Jaaskelainen, I.P., Hari, R., Sams, M., 2012. Emotions promote social interaction by synchronizing brain activity across individuals. Proc. Natl. Acad. Sci. 109, 9599–604. doi:10.1073/pnas.1206095109

Nummenmaa, L., Hirvonen, J., Parkkola, R., Hietanen, J.K., 2008. Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. NeuroImage 43, 571–80. doi:10.1016/j.neuroimage.2008.08.014

Nummenmaa, L., Hyönä, J., Calvo, M.G., 2006. Eye movement assessment of selective attentional capture by emotional pictures. Emotion 6, 257.

Nummenmaa, L., Saarimäki, H., Glerean, E., Gotsopoulos, A., Jääskeläinen, I.P., Hari, R., Sams, M., 2014b. Emotional speech synchronizes brains across listeners and engages large-scale dynamic brain networks. NeuroImage 102 Pt 2, 498–509. doi:10.1016/j.neuroimage.2014.07.063

Nummenmaa, L., Smirnov, D., Lahnakoski, J.M., Glerean, E., Jääskeläinen, I.P., Sams, M., Hari, R., 2014c. Mental action simulation synchronizes action-observation circuits across individuals. J. Neurosci. Off. J. Soc. Neurosci. 34, 748–57. doi:10.1523/JNEUROSCI.0352-13.2014

Pajula, J., Kauppi, J.-P., Tohka, J., 2012. Inter-Subject Correlation in fMRI: Method Validation against Stimulus-Model Based Analysis. PLoS ONE 8, e41196. doi:10.1371/journal.pone.0041196

Penttonen, M., Buzsáki, G., 2003. Natural logarithmic relationship between brain oscillators. Thalamus Relat. Syst. 2, 145–152.

Pitt, D., 2013. Mental Representation, in: Zalta, E.N. (Ed.), The Stanford Encyclopedia of Philosophy.

Plaza, S.M., Scheffer, L.K., Chklovskii, D.B., 2014. Toward large-scale connectome reconstructions. Curr. Opin. Neurobiol. 25, 201–10. doi:10.1016/j.conb.2014.01.019

Politis, D.N., Romano, J.P., 1992. A circular block-resampling procedure for stationary data, in: Exploring the Limits of Bootstrap. pp. 263–270.

Ponce-Alvarez, A., Deco, G., Hagmann, P., Romani, G.L., Mantini, D., Corbetta, M., 2015. Resting-State Temporal Synchronization Networks Emerge from Connectivity Topology and Heterogeneity. PLoS Comput. Biol. 11, e1004100. doi:10.1371/journal.pcbi.1004100

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 59, 2142–54. doi:10.1016/j.neuroimage.2011.10.018

Power, J.D., Cohen, A.L., Nelson, S.M., Wig, G.S., Barnes, K.A., Church, J.A., Vogel, A.C., Laumann, T.O., Miezin, F.M., Schlaggar, B.L., Petersen, S.E., 2011. Functional network organization of the human brain. Neuron 72, 665–78. doi:10.1016/j.neuron.2011.09.006

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84, 320–341.

Pruim, R.H.R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J.K., Beckmann, C.F., 2015. ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. NeuroImage 112, 267–277. doi:10.1016/j.neuroimage.2015.02.064

Raichle, M.E., 2015. The Brain's Default Mode Network. Annu. Rev. Neurosci. doi:10.1146/annurev-neuro-071013-014030

Rosenblum, M., Pikovsky, A., Kurths, J., 1996. Phase synchronization of chaotic oscillators. Phys. Rev. Lett. 76, 1804–1807.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. NeuroImage 52, 1059–69. doi:10.1016/j.neuroimage.2009.10.003

Sabuncu, M.R., Singer, B.D., Conroy, B., Bryan, R.E., Ramadge, P.J., Haxby, J.V., 2010. Function-based intersubject alignment of human cortical anatomy. Cereb. Cortex N. Y. N 1991 20, 130–40. doi:10.1093/cercor/bhp085

Salmi, J., Roine, U., Glerean, E., Lahnakoski, J., Nieminen-von Wendt, T., Tani, P., Leppämäki, S., Nummenmaa, L., Jääskeläinen, I.P., Carlson, S., Rintahaka, P., Sams, M., 2013. The brains of high functioning autistic individuals do not synchronize with those of others. NeuroImage Clin. 3, 489–97. doi:10.1016/j.nicl.2013.10.011

Sarty, G.E., 2007. Computing brain activity maps from fMRI time-series images. Cambridge University Press.

Scheinost, D., Papademetris, X., Constable, R.T., 2014. The impact of image smoothness on intrinsic functional connectivity and head motion confounds. NeuroImage 95, 13–21. doi:10.1016/j.neuroimage.2014.03.035

Schilbach, L., Timmermans, B., Reddy, V., Costall, A., Bente, G., Schlicht, T., Vogeley, K., 2013. A second-person neuroscience in interaction. Behav. Brain Sci. 36, 441–462. doi:10.1017/S0140525X12002452

Schippers, M.B., Roebroeck, A., Renken, R., Nanetti, L., Keysers, C., 2010. Mapping the information flow from one brain to another during gestural communication. Proc. Natl. Acad. Sci. U. S. A. 107, 9388–93. doi:10.1073/pnas.1001791107

Schölvinck, M.L., Maier, A., Ye, F.Q., Duyn, J.H., Leopold, D.A., 2010. Neural basis of global resting-state fMRI activity. Proc. Natl. Acad. Sci. U. S. A. 107, 10238–43. doi:10.1073/pnas.0913110107

Selfhout, M.H.W., Branje, S.J.T., ter Bogt, T.F.M., Meeus, W.H.J., 2009. The role of music preferences in early adolescents' friendship formation and stability. J. Adolesc. 32, 95–107. doi:10.1016/j.adolescence.2007.11.004

Shannon, C.E., 1949. Communication in the presence of noise. Proc. IRE 37, 10–21. doi:10.1109/JPROC.1998.659497

Shehzad, Z., Kelly, C., Reiss, P.T., Cameron Craddock, R., Emerson, J.W., McMahon, K., Copland, D.A., Castellanos, F.X., Milham, M.P., 2014. A multivariate distance-based analytic framework for connectome-wide association studies. NeuroImage 93 Pt 1, 74–94. doi:10.1016/j.neuroimage.2014.02.024

Smirnov, D., Glerean, E., Lahnakoski, J.M., Salmi, J., Jääskeläinen, I.P., Sams, M., Nummenmaa, L., 2014. Fronto-parietal network supports context-dependent speech comprehension. Neuropsychologia 63, 293–303. doi:10.1016/j.neuropsychologia.2014.09.007

Smith, A.M., Lewis, B.K., Ruttimann, U.E., Ye, F.Q., Sinnwell, T.M., Yang, Y., Duyn, J.H., Frank, J. a, 1999. Investigation of low frequency drift in fMRI signal. NeuroImage 9, 526–33. doi:10.1006/nimg.1999.0435

Smith, S.M., Miller, K.L., Salimi-Khorshidi, G., Webster, M., Beckmann, C.F., Nichols, T.E., Ramsey, J.D., Woolrich, M.W., 2011. Network modelling methods for FMRI. NeuroImage 54, 875–891. doi:10.1016/j.neuroimage.2010.08.063

Sporns, O., 2014. Contributions and challenges for network models in cognitive neuroscience. Nat. Neurosci. 17, 652–60. doi:10.1038/nn.3690

Sporns, O., 2010. Networks of the Brain. MIT Press.

Stam, C.J., 2014. Modern network science of neurological disorders. Nat. Rev. Neurosci. 15, 683–695. doi:10.1038/nrn3801

Stansbury, D.E., Naselaris, T., Gallant, J.L., 2013. Natural scene statistics account for the representation of scene categories in human visual cortex. Neuron 79, 1025–34. doi:10.1016/j.neuron.2013.06.034

Steen, M., Hayasaka, S., Joyce, K., Laurienti, P., 2011. Assessing the consistency of community structure in complex networks. Phys. Rev. E 84, 016111. doi:10.1103/PhysRevE.84.016111

Stephens, G.J., Honey, C.J., Hasson, U., 2013. A place for time: the spatiotemporal structure of neural dynamics during natural audition. J. Neurophysiol. 110, 2019–2026.

Stephens, G.J., Silbert, L.J., Hasson, U., 2010. Speaker-listener neural coupling underlies successful communication. Proc. Natl. Acad. Sci. U. S. A. 107, 14425–30. doi:10.1073/pnas.1008662107

Stolk, A., 2014. In sync: metaphor, mechanism or marker of mutual understanding? J. Neurosci. Off. J. Soc. Neurosci. 34, 5397–8. doi:10.1523/JNEUROSCI.0607-14.2014

Strogatz, S.H., 2004. Sync: the emerging science of spontaneous order. Penguin.

Supekar, K., Uddin, L.Q., Khouzam, A., Phillips, J., Gaillard, W.D., Kenworthy, L.E., Yerys, B.E., Vaidya, C.J., Menon, V., 2013. Brain hyperconnectivity in children with autism and its links to social deficits. Cell Rep. 5, 738–47. doi:10.1016/j.celrep.2013.10.001

Tagliazucchi, E., Balenzuela, P., Fraiman, D., Chialvo, D.R., 2012. Criticality in large-scale brain FMRI dynamics unveiled by a novel point process analysis. Front. Physiol. 3, 15. doi:10.3389/fphys.2012.00015

Tversky, A., 1977. Features of similarity.

Tyler, L.E., 1965. The psychology of human differences.

Van Dijk, K.R.A., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103, 297–321. doi:10.1152/jn.00783.2009

Villafane-Delgado, M., Zhu, D.C., Aviyente, S., 2014. Computation of resting state networks from fMRI through a measure of phase synchrony. Conf. Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf. 2014, 1456–9. doi:10.1109/EMBC.2014.6943875

Wang, H.X., Freeman, J., Merriam, E.P., Hasson, U., Heeger, D.J., 2012. Temporal eye movement strategies during naturalistic viewing. J. Vis. 12, 16. doi:10.1167/12.1.16

Wang, L., Saalmann, Y.B., Pinsk, M.A., Arcaro, M.J., Kastner, S., 2012. Electrophysiological low-frequency coherence and cross-frequency coupling contribute to BOLD connectivity. Neuron 76, 1010–20. doi:10.1016/j.neuron.2012.09.033

Willsey, A.J., State, M.W., 2015. Autism spectrum disorders: from genes to neurobiology. Curr. Opin. Neurobiol. 30, 92 – 99. doi:http://dx.doi.org/10.1016/j.conb.2014.10.015

Wise, R.G., Ide, K., Poulin, M.J., Tracey, I., 2004. Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal. NeuroImage 21, 1652–64. doi:10.1016/j.neuroimage.2003.11.025

Xue, S.-W., Li, D., Weng, X.-C., Northoff, G., Li, D.-W., 2014. Different Neural Manifestations of Two Slow Frequency Bands in Resting Functional Magnetic Resonance Imaging: A Systemic Survey at Regional, Interregional, and Network Levels. Brain Connect. 1–14. doi:10.1089/brain.2013.0182

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 1125–1165. doi:10.1152/jn.00338.2011

Zalesky, A., Fornito, A., Bullmore, E.T., 2010. Network-based statistic: identifying differences in brain networks. NeuroImage 53, 1197–207. doi:10.1016/j.neuroimage.2010.06.041

Zapala, M.A., Schork, N.J., 2012. Statistical properties of multivariate distance matrix regression for high-dimensional data analysis. Front. Genet. 3, 190. doi:10.3389/fgene.2012.00190

Zapala, M.A., Schork, N.J., 2006. Multivariate regression analysis of distance matrices for testing associations between gene expression patterns and related variables. Proc. Natl. Acad. Sci. U. S. A. 103, 19430–5. doi:10.1073/pnas.0609333103

Zeng, L.-L., Wang, D., Fox, M.D., Sabuncu, M., Hu, D., Ge, M., Buckner, R.L., Liu, H., 2014. Neurobiological basis of head motion in brain imaging. Proc. Natl. Acad. Sci. 111, 6058–6062. doi:10.1073/pnas.1317424111

Zhou, Y., Yu, F., Duong, T., 2014. Multiparametric MRI characterization and prediction in autism spectrum disorder using graph theory and machine learning. PloS One 9, e90405. doi:10.1371/journal.pone.0090405

Zou, Q.-H., Zhu, C.-Z., Yang, Y., Zuo, X.-N., Long, X.-Y., Cao, Q.-J., Wang, Y.-F., Zang, Y.-F., 2008. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J. Neurosci. Methods 172, 137–41. doi:10.1016/j.jneumeth.2008.04.012

Zuo, X.-N., Di Martino, A., Kelly, C., Shehzad, Z.E., Gee, D.G., Klein, D.F., Castellanos, F.X., Biswal, B.B., Milham, M.P., 2010. The oscillating brain: complex and reliable. NeuroImage 49, 1432–45. doi:10.1016/j.neuroimage.2009.09.037

What makes us similar and different? The intriguing problem has been studied throughout the centuries by philosophers and scientists and affects the way we live in relationship to the people around us. The brain processes the external world in a similar way across people and even across animal species, but the boundary between similar/different is a dynamic one that changes in space and in time. Here I studied how intersubject similarity of brain activity is modulated in time and how similar are brain subnetworks in healthy participants and individuals with autism spectrum disorder. The studies reflect recent methodological developments in human neuroscience, by stressing the importance of the temporal dimension from local activity to time-varying networks and the individuality of each brain. Mutual understanding and similarity of behaviour might be related to similarity of brain function. Although the causality of such relationships might be difficult to disentangle, the current work proposes tools to quantify them.

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